# IMPROVING CONSERVATIVE TREATMENT OF KNEE AND HIP OSTEOARTHRITIS

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# IMPROVING CONSERVATIVE TREATMENT OF KNEE AND HIP OSTEOARTHRITIS

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# 1

# GENERAL INTRODUCTION

# OSTEOARTHRITIS

Osteoarthritis (OA) is a common rheumatic disease that affects all structures of the synovial joint. Besides articular cartilage, the subchondral bone, synovial tissue and soft tissue structures around the joint may be more or less involved.[1] OA may occur in any joint, but the spine, hands, hips, knees and feet are predilection sites.[2] OA is a heterogenic, multifactorial disease with largely well-known systemic and biomechanical determinants of aetiology and progression.[3-5]

## History

The early history of OA is unclear. This is mostly because of the variation in used terminology, due to confusion with other diseases and with generalised and secondary forms of OA.[6]

From the times of Hippocrates until only 250 years ago, all forms of chronic arthritis were regarded as manifestations of gout. William Heberden the Elder (1710-1801) was the first to distinguish a form of arthritis from gout.[7] He observed small nodes (that are nowadays named after him) without connection with gout. In 1793 Sandifort of Leiden described osteoarthrosis of the hip. His contemporary John Haygarth (1805) made a description of a polyarticular disease affecting the distal interphalangeal joints and other joints, perfectly resembling OA as seen in present time. Benjamin C. Brodie, professor of surgery in London, was one of the first to appreciate a non-inflammatory erosion of articular cartilage in the elderly in 1829. A few years later, Robert Smith described malum coxae senilis. It was distinguished from polyarticular rheumatoid arthritis by its localised character, probably by Robert Adams in 1831 in Dublin. Charcot and Virchow used the term 'arthritis deformans' (1869) for both OA and rheumatoid arthritis. The disease got his current name of 'osteoarthritis' in 1890 by A.E. Garrod. After the introduction of X-rays by Wilhelm Konrad Röntgen in 1895, Goldthwaite and others were able to distinguish OA from other forms of arthritis using radiographs. Kellgren and Moore linked Heberden nodules to OA in the early 1950s. In the next decades Kellgren and Lawrence developed the nowadays used radiographic grading system of OA.[8] Only since a few decades OA is recognised as a disease that affects the whole joint, as it is nowadays.

## Pathogenesis

The homeostasis of articular cartilage is driven by chondrocytes, which produce extracellular matrix substitutes like collagens and proteoglycans as well as the cartilage degrading proteinases. OA results from the failure of chondrocytes within the joint to synthesize a good quality matrix, in terms of resistance and elasticity, and to maintain the balance between synthesis and degradation of the extracellular matrix. The change in the quality of the extracellular matrix synthesized is due to alterations in the differentiation process of chondrocytes,[9] via effects including alterations in expression of essential molecules on the chondrocytes. The imbalance between synthesis and degradation of the extracellular matrix is caused by increased production of proteinases.

Although the role of the chondrocytes seems fundamental, the synovial cells are able to activate chondrocytes and alter the extracellular matrix of articular cartilage and therefore

play a prominent role in the pathogenesis of OA as well. Finally, subchondral osteoblasts contribute to cartilage degradation. The initiation of OA is not well-understood. It involves local mechanical, systemic, genetic and environmental factors.[10]

## Epidemiology

Based on registration data from the National Public Health Compass (Nationaal Kompas Volksgezondheid) the point prevalence of symptomatic peripheral joint OA in The Netherlands is over 600,000, which makes it the third most prevalent disease after visual impairment and coronal disease.[11] Hip and knee OA affects 29/1000 and 38/1000 individuals, respectively, in The Netherlands. In the age-category of 60 to 64 years hip OA and knee OA occur in 56/1000 and 74/1000 persons, respectively. The prevalence in older individuals is even higher. Although OA is known to be an age-related disease, it is estimated that approximately 25,000 individuals aged between 25 to 44 years in The Netherlands have OA.

Risk factors for OA are usually divided in risk factors for incident disease and risk factors for progression. The most important risk factors for incident OA include ageing, congenital and developmental abnormalities, joint injury, (occupational) physical activity, and obesity. Important risk factors for OA progression include malalignment, muscle weakness, and obesity.[3-5] Due to demographical changes and the increase in overweight, an increased incidence and prevalence of OA could be expected in the near future.

## Clinical aspects

Clinically OA is characterised by joint pain, stiffness, limitation of movement, crepitus and occasionally effusion and other signs of inflammation. The pain is generally described as worsening by activity and relieving by rest, whereas joint stiffness is typically present at initiation of movement. Generally, the symptoms due to OA vary between patients, but also within patients: periods of more perceived symptoms may spontaneously be followed by periods characterized by fewer complaints. X-rays may show joint space narrowing, marginal osteophytes, subchondral sclerosis and cysts. However, radiographic changes correlate only modestly with clinical signs.[12] Therefore, the diagnosis is often made without abnormalities on X-rays.[13-15]

## Management

During the last decades major advances have been made in the understanding of the pathogenesis of OA. Consequently, efforts are being made to develop agents with disease-modifying properties, known as disease-modifying OA drugs (DMOADs).

Possible DMOADs, including drugs directed against cytokines involved in inflammation,[16;17] enzymes that degrade cartilage[18;19] and subchondral bone[20] have been investigated, mainly in knee OA. However, none has proven to be an irrefutable DMOAD yet.

Because interventions for OA with structure-modifying properties are not available at the moment, existing treatment options are directed to prevent progression and reduce symptoms. The most evidence-based treatment options exist for knee and hip

OA and comprise non-surgical and surgical interventions. The former is subdivided in non-pharmacological and pharmacological treatments.

Regarding non-pharmacological interventions for knee and hip OA, recommendations in treatment guidelines include education, lifestyle advices including regular physical activity, advices aiming for weight reduction in case of obesity and exercises directed to improvement of muscle strength and range of motion. Pharmacological treatment options are paracetamol (acetaminophen), (topical) non-steroidal anti-inflammatory drugs (NSAIDs), weak opioids and injection therapy.[21-23] The use of nutritional supplements such as glucosamine and chondroitin is obsolete.[24]

Surgical options include total joint replacement and other surgical approaches, like osteotomy and unicompartmental knee replacement. The role of joint lavage and arthroscopic debridement in knee OA is controversial.[21;25] Although total knee arthroplasty (TKA) and total hip arthroplasty (THA) are generally accepted as approaches to restore function and health-related quality of life in knee and hip OA patients, the utility is limited to some extent due to the frequent need for revision surgery after 10 to 15 years. Therefore, joint replacement is unattractive in relatively young knee and hip OA patients and joint replacement should in those cases be delayed as long as possible. Other drawbacks for joint replacement surgery are perioperative complications and persisting complaints in 10 to 15% of patients.[26]

It is generally recommended that joint replacement surgery should be reserved for individuals insufficiently responding to conservative treatment options.[21-23] However, patients with knee or hip OA often have not been offered even minimum recommended conservative treatment.[27] In addition, adherence to the widely available evidence-based treatment guidelines for knee and hip OA is often poor.[28] Also, patients on a waiting list for a TKA or THA consume less health care,[29] possibly indicating underuse of conservative treatment options.

Due to the aforementioned drawbacks of joint replacement surgery in addition to the high costs of this approach and the long time patients do have OA-related symptoms until joint replacement, effective conservative treatment options and adherence to existing evidence-based treatment guidelines for knee and hip OA are essential. Moreover, the annual number of TKA's and THA's increased with 50 to 200% between 1995 and 2005 in The Netherlands and is expected to increase further in the near future,[30] indicating increasing incidence of OA and failure and/or underuse of conservative treatment. This underlines the need for optimizing conservative treatment of knee and hip OA.

## OUTLINE OF THIS THESIS

Because effective conservative treatment is highly needed, this thesis focuses on better use of existing conservative treatment options in addition to studying possible new treatment targets in the conservative treatment of knee and hip OA. The content of the chapters in this thesis is outlined below.

In **Chapter 2**, a study describing OA-related health care and predictors for future health care utilization (HCU) in a cohort of early knee and hip OA (Cohort Heup En Cohort Knee, Cohort Hip and Cohort Knee, CHECK[31]) is described. For this study, baseline and two-year data from the CHECK study were used.

In **Chapter 3**, a randomised controlled trial (RCT) of doxycycline in knee OA is presented. Doxycycline is one of the drugs with putative disease-modifying properties in OA as in one study it has shown to inhibit radiographic progression of knee OA.[18] However, the clinically important question if doxycycline exhibits symptom-modifying properties was not answered. Therefore, the effects of 24 weeks doxycycline on reducing symptoms in symptomatic knee OA were investigated.

Although individual interventions on non-surgical management as recommended by the aforementioned guidelines for knee and hip OA have been shown to be effective, insufficient data are available on the efficacy of a combination of these interventions. In addition, no information is available about possible predictors for response. Therefore, a 12-week standardised treatment protocol was developed, based on the aforementioned guidelines. The results of treatment according to this protocol and predictors for response to treatment in patients with knee and hip OA referred to secondary care are described in **Chapter 4**.

Because there are no data on the optimal strategy regarding analgesics in the treatment of symptomatic knee and hip OA, a study was initiated to explore the treatment outcome of a numeric rating scale (NRS)-guided pharmacological pain management strategy using paracetamol and NSAIDs (**Chapter 5**). Moreover, predictors for response to paracetamol and NSAIDs were identified.

Besides pain, stiffness and functional decline, patients with OA frequently complain about fatigue. In **Chapter 6**, a study is described investigating the levels of fatigue in knee and hip OA patients, assessing change in fatigue after standardised evidence-based conservative treatment and studying the cross-sectional and longitudinal relationships between fatigue with pain and daily functioning in patients with knee or hip OA.

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# 2

# PREDICTORS OF HEALTH CARE UTILIZATION IN PATIENTS WITH EARLY OSTEOARTHRITIS: RESULTS FROM THE CHECK COHORT

# ABSTRACT

**Introduction** Identifying (modifiable) factors that predispose individuals with osteoarthritis (OA) for atypical patterns of health care utilization (HCU) (i.e. 'persistent non-users' or 'high-users' of health care), could help health professionals to optimize a patients' use of the health care system. Therefore, we aim to describe and predict HCU over time in individuals with early symptomatic hip and/or knee OA.

**Methods** Baseline and two-year data on HCU of the 1002 participants with early symptomatic hip and knee OA from the Cohort Hip and Cohort Knee (CHECK) study were used. Six forms of health care services were distinguished: use of analgesics and/or supplements, contact with a general practitioner, an allied health professional, secondary care or alternative care. By use of median split, high overall users of health care were identified. Participants without HCU at baseline and two years were labelled persistent non-users. Multiple imputation was used to handle missing data. Multivariate logistic regression was performed to identify predisposing, enabling and disease-related variables that could predict either high overall health care use at two years or persistent non-use of health care.

**Results** No relevant differences in HCU between participants with early hip OA (n=588) and participants with knee OA (n=832) were found. After two years of follow-up, contact with health care providers decreased in both groups, whereas use of analgesics remained stable. Compromised physical health and baseline use of health care were the strongest predictors for future high overall HCU in both the knee (Nagelkerke's $R^2$: 0.27) and hip group (Nagelkerke's $R^2$: 0.25). The strongest predictors for persistent non-use of health care were lower levels of joint stiffness and better physical health in both the knee (Nagelkerke's $R^2$: 0.23) and hip group (Nagelkerke's $R^2$ = 0.24).

**Conclusion** At two years, the majority of participants with early symptomatic hip and/or knee OA reported HCU for their OA complaints. To some extent future low or high-use of the health care system is predictable. No enabling factors were longitudinally associated with HCU, which suggest equity in health care for OA in The Netherlands.



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# INTRODUCTION

Individuals with osteoarthritis (OA) often require long-term access to a broad range of health care services.[1;2] Numerous cross-sectional studies have shown much variability in the amount of health care utilization (HCU) in people with OA.[3-14] Moreover, a number of characteristics have been found to be cross-sectionally associated with higher HCU in people with OA, including obesity, being single, higher education, pain, disabilities, depression, quality of life, comorbidities and previous HCU.[3;4;7-12;14]

It could be of value to describe HCU over time in OA patients and identify (modifiable) longitudinally associated risk factors for the use of OA-related care. Understanding factors that predispose patients as (persistent) non-users or high-users of the health care system, could allow health care providers and/or policy makers to intervene and possibly optimize patients' use of health care resources. To date, however, longitudinal research on OA related HCU is scarce[15;16] and no predictors of future HCU in individuals with OA are available. Another hiatus in the current body of HCU evidence is the lack of studies describing health care consumption of individuals with early OA, whereas we believe patients in the earliest phase of the disease could and should be guided throughout the plethora of different treatment options.

According to the model of Andersen and Newman, access to health care depends on three types of factors: predisposing factors, enabling factors, and disease-related factors.[17;18] Predisposing characteristics refer to demographic and social characteristics. Enabling resources reflect the ability to use care resources. Disease-related factors represent the most immediate cause for HCU, reflected by diagnosis, perception of illness, presence of symptoms, and disability.[19] This model can be used to find evidence for equity or inequity in access to health care. Equity is demonstrated when care is primarily determined by health-related need factors and inequity is demonstrated when care is merely explained by enabling resources.[19]

The aims of this study were 1) to describe HCU and 2) to identify predictors (i.e. predisposing, enabling and disease-related) for future persistent non-use and high-use of OA-related health care services in individuals with early symptomatic hip and/or knee OA. To do so, we used baseline and two-year follow-up data on HCU from the Cohort Hip and Cohort Knee (CHECK) cohort,[20] that describes participants with early symptomatic hip and/or knee OA.

# PATIENTS AND METHODS

## Design

Baseline and two year follow-up data were used from the CHECK cohort.[20] CHECK is a prospective cohort study of 1002 individuals with early symptomatic OA of hip and/or knee in The Netherlands. These individuals will be followed prospectively for a total period of 10 years. A total of 10 general and university hospitals are participating. Eligibility was checked by physicians of participating centres. Study visits for all participants were planned

at baseline and at two, five, eight and 10 years and consist of structured interview, physical examination, radiological assessment, serum- and urine-analysis, and questionnaires.

The study was approved by the medical ethics committees of all participating centres and all participants gave their written informed consent. Data on self-report and physical examination at baseline and two year data on HCU from the CHECK cohort were used for the current study.

## Study population

On entry, all participants had pain or stiffness of hip and/or knee, and were aged 45-65 years. They had not yet consulted their physician for these symptoms, or the first consultation was within 6 months before entry. Participants with any other pathological condition that could explain the symptoms were excluded (e.g. other rheumatic disease, previous hip or knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, Perthes' disease, ligament or meniscus damage, plica syndrome, Baker's cyst).

For our analyses, a hip group (n = 588) and a knee group (n = 832) were defined, based on self-reported joint pain by the participants during the first study visit. Individuals with both hip and knee pain were included in both groups, to reflect the typical knee and hip OA population.[21;22]

## Outcome measure

*Health care utilization (dependent variable)*

A HCU questionnaire was developed based on the one developed by Patient Panel Chronic Diseases (The Netherlands Institute for Health Services Research; NIVEL)[23] and the questionnaire Economic Aspects in Rheumatoid Arthritis.[24] Participants reported whether or not they had visited health care providers during the last three months or were hospitalized during the last year for their hip and/or knee problems. All available OA-related health care services were included: the general practitioner (GP), medical specialists (e.g. rheumatologist, orthopaedic surgeon), allied health professionals (i.e. physiotherapy, occupational therapy, exercise therapy, psychology), hospital stay, use of analgesics (i.e. prescription and over-the-counter drugs) and/or supplements (i.e. glucosamine and/or chondroitin), and 'complementary and alternative medicine' (CAM).

*Prognostic factors (independent variables)*

Patient characteristic (sociodemographic data, lifestyle factors) and comorbidity were collected by use of a standardised questionnaire.

Patient-reported outcome measures were determined by use of validated questionnaires. Pain over the last week was measured with a numeric rating scale (NRS, 0-10).[25] Condition specific health status was evaluated with the WOMAC.[26;27] WOMAC evaluates three dimensions, pain (0-20), stiffness (0-8), and physical function (0-68), where higher scores represent worse health status. Self-reported health related quality of life was measured using the Short Form 36 (SF-36) health survey.[28] The SF-36 consists of eighth subscales with a score range of 0-100, where 100 represents the best possible

health situation. The physical (PCS) and mental component summary (MCS) scores were calculated and fatigue and distress were assessed with the Vitality and Mental Health subscale of the SF-36, respectively.[28] Coping behaviour was measured with the Pain Coping Inventory.[29;30] Active coping was defined as the mean of three active strategies (pain transformation, distraction, and reducing demands) and passive coping as the mean of three passive strategy scores (retreating, worrying and resting). Value of own health was assessed with the visual analogue scale for health of the EuroQoL-5D questionnaire.[31] Social support was measured with the Dutch Social Support Scale.[32]

Physical examination of the hip consisted of measuring range of motion (internal rotation and flexion, in degrees) and pain (yes/no) during internal rotation and flexion. For the knee physical examination consisted of range of motion (flexion-extension), pain during flexion, bony tenderness, hydrops (refill test), crepitus, palpable warmth, and bony enlargement. The highest Kellgren-Lawrence Grading Scale score (range 0-4) of the two knees and two hips,[33] was used as indicator for radiological severity.

In Box 1 all prognostic variables are depicted according to the classification of Andersen and Newman,[17;18] namely predisposing factors, enabling factors, and disease-related factors.

**Box 1.** Prognostic variables categorised according to the model of Andersen and Newman.

**Predisposing factors**

Age; Sex; BMI; Ethnicity; Marital State; Education; Family Size, Work; Smoking; Alcohol consumption; Coping Style (Active & Passive); Previous HCU.

**Enabling factors**

Dependency on others; Social Support; Health insurance

**Disease-related factors**

Comorbidity; Pain during last week; Number of painful joints (hip/knee); WOMAC Pain, WOMAC Stiffness, and WOMAC Physical Function; EQ-VAS; Distress (SF-36 Mental Health), Fatigue (SF-36 Vitality); Physical health (SF-36 Physical Component Score); Mental health (SF-36 Mental Component Score); ESR.

Hip specific: Knee pain; ROM (internal rotation); ROM (Flexion); Pain during internal rotation; Pain during flexion; Highest K&L grade hip.
Knee specific: Hip pain; Palpable warmth; Bony tenderness; Hydrops; Bony enlargement; Crepitus; ROM (flexion minus extension); Pain during flexion; Highest K&L grade knee.

**BMI** body mass index; **EQ-VAS** EuroQol Visual Analogue Scale; **ESR** erythrocyte sedimentation rate; **HCU** health care utilization; **K&L** Kellgren and Lawrence; **ROM** Range of motion; **SF-36** Short Form 36, **WOMAC** Western Ontario and McMasters University Osteoarthritis index

## Statistical analysis

Statistical analyses were performed using STATA/IC 10.1 for Windows. Missing of data was described using descriptive analyses and missing data mechanisms were studied by means of indicator variables for missing values.[34;35] Logistic regression models with the indicator variable as outcome and the other variables as covariates, showed that missing data was not associated to observed values, indicating that the missing values were at least partly missing at random (MAR) and imputation of the missing values may reduce bias.[36] Multiple imputation using Imputation by Chained Equation (ICE) was used to estimate missing values.[37] All available predictor variables were used for imputation. A total of 10 multiple imputed datasets were generated.

For all descriptive analyses, complete-case data were used. Differences in HCU between participants with symptomatic hip and knee OA were evaluated with chi-square tests.

We distinguished the following six categories of health care services: 1) contact with GP, 2) contact with allied health professional, 3) contact in secondary care (i.e. contact with medical specialist and/or hospital stay), 4) use of analgesics, 5) use of supplements, and 6) use of CAM. In this study we aimed to identify predictors for (persistent) non-use of care and high-use of the health care system. To do so, we defined patients as persistent non-users of health care (yes/no) when they reported no utilization of any of the abovementioned health services both at baseline and at two years. Furthermore, we defined high-users of health care (yes/no) using the median split method on the number of health care modalities used. The median split method has been used in previous exploratory studies to distinct between high and low use of health care.[19]

Multivariable logistic regression models were built to predict persistent non-users and high-users of health care according to the statistical methods described by Holla *et al*.[38] Independent variables were selected in five steps. Step one: the individual bivariate association of each independent variable with both dependent variables was studied by calculation of odds ratio (OR) and visual inspection of graphs plotting the continuous independent variables and the logit of the dependent variable. Step two: variables identified at step one with a $p$-value < 0.20 were tested for collinearity by use of the Variance Inflation Factor (VIF, cut-off >10) statistic.[39] Step three: for each of the remaining variables from step two, logistic regression analyses were performed separately for the predefined three blocks of related factors (described above). Step four: possible prognostic factors identified at step three with a $p$-value < 0.20 were entered per block (i.e. predisposing, enabling and disease-related) into a backward stepwise regression model ($p$ removal 0.10). Step five: the prognostic factors identified in step four were entered as one block into a backward stepwise regression model ($p$ removal 0.10) to come to the final model.[38] Multi-category dummy variables were included in the next step of the model building process when at least one of the set of dummy variables was significantly related to the outcome. Finally, ORs, Hosmer and Lemeshow goodness of fit test, Area Under the Receiver Operating Curve (AUC), and Nagelkerke's $R^2$ statistic were calculated. All logistic regression analyses were repeated on each of the imputed datasets, producing ten sets of results that were combined using Rubin's rule of combination.[40] Sensitivity analyses were performed on the complete case data.

# RESULTS

## Study sample

Of the 1002 participants included at baseline, 982 (98%) participants completed the baseline questionnaire and 932 (93%) participants completed the health service questionnaire after two years. Of the 832 participants in the knee group, 602 (72%) had complete data and 750 (90%) had less than three missing values. Of the 588 participants in the hip group, 452 (77%) had complete data and 527 (90%) had less than three missing values. Knee range of motion (knee group) and erythrocyte sedimentation rate (ESR) (hip group) were the independent variables with the largest number of missing values; n=76 (9%) and n=31 (5%), respectively.

Characteristics of the study sample are presented in Table 1; for a more detailed description of the total population see Wesseling *et al* (2008).[20] We found no statistical significant differences between the hip and knee group.

**Table 1.** Demographic and disease characteristics at baseline, presented for the hip and knee group.

| | | **Hip group** | **Knee group** |
|---|---|---|---|
| n | | 588 | 832 |
| Age (mean (SD)) | | 56 (5) | 56 (5) |
| Female | | 81% | 80% |
| BMI (median (IQR)) | | 25 (23 – 28) | 26 (24 – 28) |
| Married/Partnership | Yes | 83% | 87% |
| | No | 17% | 13% |
| Education | Primary | 2% | 3% |
| | Secondary | 71% | 71% |
| | High professional education/ university | 27% | 26% |
| Highest K&L score | 0 | 75% | 66% |
| | 1 | 17% | 27% |
| | 2 | 9% | 7% |
| | 3 | 1% | 1% |
| | 4 | NA | NA |
| WOMAC (median (IQR)) | | | |
| | Pain (range 0 – 20) | 5 (3 – 8) | 5 (2 – 7) |
| | Stiffness (range 0 – 8) | 3 (2 – 4) | 3 (2 – 4) |
| | Physical function (0 – 68) | 16 (8 – 25) | 14 (7 – 23) |

**BMI** body mass index; **IQR** interquartile range; **K&L** Kellgren-Lawrence Grading Scale; **NA** not available/applicable; **SD** standard deviation; **WOMAC** Western Ontario and McMaster Universities osteoarthritis index

## Health care utilization (HCU)

Use of analgesics was the most frequently reported treatment modality at baseline (38%) and two years (40%) (Table 2). Contact with a GP (37%) and contact with an allied health care provider (20%) were the second and third most reported health care modalities at baseline and respectively third (13%) and second (17%) at two year follow-up. For almost all health care modalities a decrease or a standstill in use was observed at two years compared to baseline, except for the use of supplements (17% increase). Use of secondary care is reported by 124 (12%) participants at baseline and 71 (7%) participants at two years. Of these secondary care users, 35% reported no analgesics use at baseline nor at two years. Moreover, 44% of secondary care users reported no physical therapy use at baseline nor two years.

We found significant differences between the hip and knee group, for the number of participants that used analgesics at baseline (44% vs. 38%, respectively; p = 0.024) and at two years (47% vs. 41%, respectively; p = 0.019). The number of participants that had no HCU in two years, was significantly greater in the knee group than the hip group (50% vs. 43% respectively; p = 0.013).

## Predictors for HCU in participants with hip symptoms

A total of 237 (40%) individuals were classified as high-users of care and 102 individuals as persistent non-users of care (17%). Three predisposing factors and two disease-related factors for high-use of overall health care at two-year follow-up were identified (Nagelkerke's $R^2$: 0.25) (Table 3). Risk factors for high-use of care were previous HCU and being widow/widower. Smoking, good physical health and greater hip flexion were protective factors for being a high-user of care. Strongest predictors were HCU and baseline and physical health.

**Table 2.** Health care utilization at baseline and two years for the hip and knee group.

| | **Hip group (n=588)** | | | **Knee group (n=832)** | | |
|---|---|---|---|---|---|---|
| | **Baseline (T0) (*cc=577*)** | **Two years (T2) (*cc=547*)** | **Not at T0 & T2 (*cc=537*)** | **Baseline (T0) (*cc=814*)** | **Two years (T2) (*cc=775*)** | **Not at T0 & T2 (*cc=761*)** |
| Contact GP | 36% | 15% | 58% | 37% | 14% | 58% |
| Contact secondary care | 12% | 9% | 80% | 13% | 7% | 82% |
| Contact AHP | 22% | 20% | 66% | 19% | 16% | 71% |
| Analgesics | 44%† | 47%† | 42% | 38% | 41% | 48% |
| Glucosamine / Chondroitin | 17% | 33% | 62% | 15% | 32% | 63% |
| CAM | 14% | 11% | 82% | 10% | 9% | 86% |

† = significantly different ($p$<0.05) from knee group. **AHP** allied health provider; **CAM** complementary and alternative medicine; **cc** complete cases; **GP** general practitioner

**Table 3.** Baseline factors associated with high-/ non-use of HCU at 2-year in the hip group (n=588).

| **Predictor (*actual range*, if applicable)** | **High overall user (n = 237)** | **Persistent non-user (n = 102)** |
|---|---|---|
| Health utilization, T0 (*0 – 6*) | 1.59*** [1.35, 1.86] | NA |
| Marital state | - | - |
| Unmarried | Reference | - |
| Married/living partnership | 3.08 [0.93, 10.19] | - |
| Widow/Widower | 5.23* [1.05, 26.02] | - |
| Divorced | 2.55 [0.66, 9.81] | - |
| Smoking | 0.51* [0.28, 0.95] | - |
| Comorbidity (*0 – 4*) | - | 0.81 [0.65, 1.01] |
| Stiffness (*0 – 8*) | - | 0.73*** [0.62, 0.87] |
| Physical Health£ (*11 – 68*) | 0.96*** [0.94, 0.98] | 1.07*** [1.04, 1.11] |
| Hip flexion, degrees (*70 - 143*) | 0.98* [0.96, 0.99] | 1.04** [1.01, 1.06] |
| AUC | 0.76 [0.72, 0.80] | 0.79 [0.74, 0.84] |
| Nagelkerke's $R^2$ | 0.25 | 0.24 |
| Hosmer-Lemeshow statistic | 6.51; $p = 0.59$ | 8.56; $p = 0.43$ |

Odds Ratio; 95% confidence intervals in brackets. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. £ = Physical Component Scale, SF-36 (range 4-71). **AUC** area under the receiver operating characteristic curve; **NA** not applicable; **T0** baseline.

For persistent non-use of health care four disease-related factors were identified. Patients with additional comorbidity and higher levels of joint stiffness were less likely to be persistent non-users of health care. Patients with better physical health and greater hip range of motion were more likely to be persistent non-users of care. Joint stiffness and physical health were the strongest predictors for persistent non-use of care.

## Predictors for HCU in participants with knee symptoms

Of the 832 individuals with early symptomatic knee OA, 291 (35%) were categorised as high-users of health care and 167 (20%) as persistent non-users of care. Multivariable logistic modelling resulted in three predisposing and five disease-related factors that independently predicted high overall health care use at two-years (Nagelkerke's $R^2$: 0.27) (Table 4). Risk factors for high-use of care were previous HCU, body mass index (BMI), active coping, additional hip pain, pain during last week, and palpable warmth. Protective factors were lower levels of distress and better physical health. HCU at baseline and physical health were found to be the strongest predictors for high-use of the health system.

For persistent non-use of health care one predisposing, one enabling and six disease-related factors were identified (Nagelkerke's $R^2$: 0.23). Better physical health, better mental health, and greater range of knee motion were longitudinally associated with persistent

**Table 4.** Baseline factors associated with high-/ non-use of HCU at 2-year in the knee group (n=832).

| **Predictor (*actual range*, if applicable)** | **High overall user (n = 291)** | **Persistent non-user (n = 167)** |
|---|---|---|
| Health utilization, T0 (*0 – 6*) | 1.57*** [1.37, 1.81] | N/A |
| Body Mass Index (*13 – 43*) | 1.05* [1.01, 1.09] | - |
| Dependency on others | - | 0.35* [0.13, 0.94] |
| Active coping (*1 – 4*) | 1.53* [1.04, 2.23] | 0.65 [0.42, 1.00] |
| Hip pain | 1.64** [1.17, 2.29] | 0.65* [0.44, 0.97] |
| Pain during the last week (*0 – 10*) | 1.10* [1.00, 1.20] | - |
| Stiffness WOMAC (*0 – 8*) | - | 0.81** [0.71, 0.93] |
| Distress¥ (*16 – 100*) | 0.99* [0.98, 1.00] | |
| Physical health£ (*11 – 69*) | 0.97*** [0.95, 0.99] | 1.08*** [1.04, 1.11] |
| Mental health¶ (*6 – 70*) | | 1.04** [1.01, 1.06] |
| Knee ROM, degrees (*58 – 155*) | - | 1.03** [1.01, 1.06] |
| Hydrops | - | 0.49 [0.24, 1.03] |
| Palpable warmth | 1.91 [0.99, 3.71] | - |
| AUC | 0.77 [0.73, 0.81] | 0.77 [0.73, 0.81] |
| Nagelkerke's $R^2$ | 0.27 | 0.23 |
| Hosmer-Lemeshow statistic | 7.20; $p = 0.53$ | 4.30; $p = 0.81$ |

Odds Ratio; 95% confidence intervals in brackets. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. £ = Physical Component Scale, SF-36. ¥ = subscale Mental Health, SF-36. ¶ = Mental Component Scale, SF-36. **AUC** area under the receiver operating characteristic curve; **N/A** not applicable; **ROM** range of motion; **T0** baseline.

non-use of care. Active coping, dependency on others, additional hip pain, higher levels of stiffness, and the presence of synovial effusion were longitudinally associated with not being a persistent non-user of health care. Physical health was found to be the strongest predictor for persistent non-use of the health system.

## Sensitivity analyses

In the knee group, complete case analyses (n=672) yielded similar prediction variables as the analyses on imputed data for both dependent variables, with exception of the following: 1) mental health and palpable warmth were no predictors for high overall use of care and 2) additional hip pain was and crepitus of the knee was not a predictor for persistent non-use of health care.

In the hip group, complete case analyses were comparable to the imputed analyses for both high overall use (n=520) and persistent non-use (n=506). Exceptions being, that being/been in a partnership was not found to be an independent predictor for high overall use and 'pain during flexion' was an additional predictor for persistent non-use of care.

## DISCUSSION

In this longitudinal study we found that the majority of participants with early symptomatic hip and knee OA reported health care consumption at baseline and at two years. No relevant differences were seen in the amount of HCU between individuals with symptomatic hip and knee OA. We identified several factors that were longitudinally associated with high-use and persistent non-use of the health care system. Previous use of the health system and compromised physical health were the strongest predictors for future high-use of OA-related health care. Less joint stiffness, better physical health and greater range of motion were the strongest predictors for persistent non-use of the health care system.

As far as we know, we are the first to identify predictors for HCU in individuals with early hip or knee OA. Few studies have investigated health care consumption over time in patients with (symptomatic) hip or knee OA.[15;16] Linsell *et al* (2005) showed in a three-year, record-based follow-up study of 1410 symptomatic hip and 3152 symptomatic knee OA cases, that hip cases were referred to a specialist significantly more often (38 versus 32%) and that knee cases were more often managed using conservative treatment modalities.[15] Our results are not in line with the results of this study, as we found that individuals with hip complaints more frequently reported use of analgesics than patients with knee complaints. Moreover, we also found a much lower rate of referrals to secondary care (9% and 7% respectively for hip and knee). This discrepancy might be explained by differences in time frame of the studies, sampling methods and management of OA among different countries.

Strengths of our study include the large sample size and the fact that 10 different centres participated. The original response rate was very high (98%) as were retention rates. In addition, the amount of missing data was small. Limitations include the reliance on self-report data with regard to HCU which may have induced recall bias, which most likely resulted in overreporting.[41] On the other hand, participants may have reported the contact with the assessor (allied health professional or clinician) as health consumption, which could have resulted in a slight overreporting of health care contacts. A second limitation is that participants in the CHECK cohort may have regarded the CHECK visits as a substitute for contacts with other care providers, thus possibly resulting in less utilization of health care. Third, the cohort is formed in The Netherlands, which affects - to some extent - the study's generalisability, due to its specific health care system. In The Netherlands, GPs are accessible for everyone since basic health insurance is mandatory. Insurers are obligated to offer a package with state-controlled insured treatments and may offer additional optional health insurance packages at extra costs. Dutch primary care, with gatekeeping GPs at its core, prevents unnecessary use of more expensive secondary care, and promotes consistency and coordination of individual care. It is likely that the results in this study are particularly generalisable to countries with a similar health care system, such as the United Kingdom, Spain, Finland and Italy. Finally, the overlap in our findings about HCU in participants with hip and participants with knee symptoms could have been caused by the overlap in data of patients used in both the hip and knee analyses. On the other hand, involvement of multiple joints in the disease process of OA is very common, particularly in the elderly. We therefore believe that the overlap in our samples does represent the typical knee and hip OA population.

Supplement use (i.e. glucosamine and chondroitin) was the only treatment modality that increased over the two year period. We could not find a satisfactory explanation for this. The CHECK cohort was formed from 2002 till 2005 and glucosamine was registered in The Netherlands as an over-the-counter drug in 2005, although it was available before that. This registration, however, hardly increased overall supplement use during that period in The Netherlands. Another hypothesis for this increase could be that patients try other, more alternative forms of care, after experiencing disappointing results from conventional treatments. However, this explanation is questionable since other forms of alternative care decreased over the two year period. Moreover, additional post-hoc analyses in our dataset did not support this hypothesis (data not shown). Additional long-term observation of supplement use in the CHECK cohort will reveal whether this is a persisting increase.

The model of Andersen and Newman is often used to find evidence for equity or inequity in access to health care. When care is primarily determined by health-related need factors, equity of care can be assumed, since patients receive the care tailored to their needs. When care is merely explained by enabling resources, inequity of care is demonstrated. In our study, the majority of prognostic factors in our prediction models were disease-related and to a lesser extent predisposing factors. Following the latter reason of deduction, we can state that there is equity in the access to health care system in The Netherlands for people suffering from early symptomatic OA.

An unexpected finding in our study was that smoking was a protective factor for HCU over time in hip pain, since smoking is generally associated with an increase in HCU.[42] This counterintuitive, protective effect has also been reported in other areas of the disease. In a recent systematic review, smoking appeared to have a moderate protective effect for the risk of knee OA.[43] However, the validity of this finding is under debate as this result was not apparent when restricting the analysis to cohort studies.[44]

In conclusion, the results of our study demonstrate that HCU remains stable over a period of two years and that there is equity in the access to health care services for patients with early symptomatic OA of the hip or knee. Previous use of the health system and compromised physical health were strongest predictors for future high-use of OA-related health care. Less joint stiffness, better physical health and greater range of motion were the strongest predictors for persistent non-use of the health care system.

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# 3

# THE EFFECTS OF DOXYCYCLINE ON REDUCING SYMPTOMS IN KNEE OSTEOARTHRITIS: RESULTS FROM A TRIPLE-BLINDED RANDOMISED CONTROLLED TRIAL

# ABSTRACT

**Objectives** Evidence suggests that doxycycline might have disease-modifying properties in osteoarthritis (OA). However, the clinically relevant question as to whether doxycycline also modifies symptoms in knee OA is unanswered. The objective of this study was to investigate the effectiveness of doxycycline on pain and daily functioning in symptomatic knee OA.

**Methods** A 24-week, randomised, triple-blind, placebo controlled trial on the symptomatic effectiveness of doxycycline twice a day 100 mg in knee OA patients according to the clinical and radiological American College of Rheumatology (ACR) classification criteria. The primary endpoint was the difference in the proportion of participants in both study groups achieving a clinical response defined by the OMERACT-OARSI set of responder criteria. Secondary endpoints included pain, stiffness, daily functioning, patient global assessment, quality of life, OA-related medication and side effects.

**Results** 232 patients were randomly assigned. At study end, 31% of participants met the primary endpoint in both groups. Except for more adverse events in the doxycycline group, no differences were found on the secondary endpoints.

**Conclusion** Doxycycline is not effective in reducing symptoms in knee OA patients over a 24-week study period, but is associated with increased risk of adverse events. Although a possible structure-modifying effect of doxycycline was previously suggested, this is not accompanied by symptom relief in the short and medium term.

Dutch Trial Register number: NTR1111.



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# INTRODUCTION

The search for a disease-modifying osteoarthritis drug (DMOAD) for osteoarthritis (OA) targeting both symptoms and structure has been intensified in recent years. Several studies investigating candidate DMOADs in clinical trials have been published, including dietary supplements, diacerein, strontium ranalate, bisphosphonates, biologics, autologous conditioned serum, calcitonin and doxycycline.[1-18]

However, up to now, no agent is known to be an irrefutable confirmed DMOAD as results of most studies remain largely ambiguous or difficult to interpret. For diacerein, risedronate, calcitonin and autologous conditioned serum the efficacy on symptoms have been demonstrated in randomised controlled trials (RCTs), but these results have thus far not been confirmed in more than one study, except for diacerein. Effects on structural change have been shown for risedronate, diacerein and doxycycline,[5;12;13] although these results have not been replicated successfully thus far.[19] Whether doxycycline also modifies symptoms of OA has not yet been established.

Doxycycline is a tetracycline class antibiotic agent. Besides being an antimicrobial agent, it is a metalloproteinase inhibitor and inhibits the collagenase that cleaves collagen type IX that is present in the articular cartilage.[20-22] Doxycycline has been studied in human OA in one clinical trial, in which doxycycline was found to retard progression of radiographic knee OA.[13] The original intent of this study was to assess the efficacy of doxycycline to retard progression and prevent the occurrence of radiographic knee OA in overweight female patients with unilateral radiographic knee OA. However, although the contralateral knee was radiographically normal in the conventional anterior-posterior (AP) view, in most cases there was evidence for OA in the lateral, semiflexed AP and/or patellofemoral view. Therefore, de facto the effect of doxycycline on the progression of less extensive OA in that joint was assessed. Although no effect on less extensive knee OA was seen, radiographic progression was substantially slower in the knee with established OA. No effect on pain was found, presumably due to low pain scores at enrolment. However, post-hoc analyses demonstrated lower incidences of increased pain (> 20% increase in pain score) in the index knee but not in the non-affected knee. Also, side effects were mild and drop-out due to possible side effects of doxycycline was rare (~ 8%) during the 30-month trial period.

Although a proof of principle of DMOAD properties of doxycycline has thus been demonstrated, the clinically relevant question as to whether doxycycline also reduces pain and improves daily functioning in symptomatic knee OA has not been answered.

To explore the effects of doxycycline on reducing symptoms in knee OA, a 24-week triple-blinded, randomised, placebo controlled trial was conducted to evaluate the effect of doxycycline on pain and daily functioning in well established knee OA.

# PATIENTS AND METHODS

## Study design

This triple-blinded, randomised, placebo controlled trial was performed as a mono-centre study in the Sint Maartenskliniek, Nijmegen, The Netherlands. The local Medical Research Ethics Committee, region Arnhem/Nijmegen, The Netherlands, and the national Central Committee on Research involving Human Subjects (CCMO) approved the study. Moreover, the study was registered at EUDRACT and in the Dutch Trial Register (www.trialregister.nl; trial number: NTR1111). All participants gave their informed consent.

## Participants

Patients were eligible for inclusion if they met the following criteria: fulfilment of the clinical and radiological American College of Rheumatology (ACR) classification criteria for knee OA[23] in the index knee (defined as the knee causing most complaints during the screening visit), Kellgren-Lawrence (K&L) score 2 or 3[24], Knee injury and Osteoarthritis Outcome Score (KOOS)-derived Western Ontario McMaster Universities (WOMAC) score pain subscale (see details below) of greater than 20/100 and the ability to read and communicate well in Dutch. Exclusion criteria were: inflammatory rheumatic diseases or deposition diseases possibly leading to inflammatory arthritis or secondary OA, extensive orthopaedic abnormalities (e.g. major malalignment (> 5°)), co-morbidity exceeding complaints of limitations of the knee, cognitive or sensomotor problems interfering with the use of questionnaires or intake of study medication, planned other major interventions within 24 weeks (including lower limb surgery and intensive multidisciplinary approaches), hip prosthesis in situ on the side of the symptomatic knee, contraindications for doxycycline use, such as allergy for tetracyclines and previous possible adequate treatment with doxycycline (> 100 mg/day for > 6 weeks for OA), recent intra-articular hyaluronic acid/corticosteroid application or arthroscopy (< 3 months) or open surgical procedures (< 1 year) in the index knee.

Participants were allowed to use analgesics during the study period, but they were asked to stop these agents during the last 48 hours and/or four times the drugs half-life before the study visits at the outpatient clinic (baseline, weeks 12 and 24). Opioids other than tramadol (up to 150 mg/day) were not allowed.

Participants were recruited from the rheumatology and orthopaedics outpatient clinics and from advertisements in local newspapers.

## Setting

All visits and collection of data took place at the Rheumatology outpatient clinic of the Sint Maartenskliniek, Nijmegen, The Netherlands, a hospital specialising in rheumatology, orthopaedics and rehabilitation.

## Randomisation and intervention

Eligible patients were randomly assigned (allocation ratio 1:1) to receive either 100 mg of oral doxycycline monohydrate or placebo twice a day (one in the morning and one in the

evening) for 24 weeks. The allocation was blinded for patient and study physician (GS) using placebo medication capsules, blue and white, with the same appearance as verum. Participants who violated the study protocol were encouraged to adhere to study visits to limit loss to follow-up.

An independent pharmacist used a computer-generated, blinded randomisation list to assign patients randomly to doxycycline or placebo. Allocation data was stored at the hospital pharmacy in sealed envelopes that could be opened in case of medical need. To increase balance in possible confounders, allocation was stratified for intensity of pain (moderate vs. severe, i.e. < 60 vs. ≥ 60 on the WOMAC pain subscale, respectively) at the screening visit using stratified block randomisation. Assignment of patients to the right stratum of the random assignment-list was performed by the study physician (GS) who was blinded to therapy.



## Assessments

Visits were planned at screening (week -2), baseline, weeks 12 and 24 at the outpatient clinic and in weeks 6 and 18 by telephone. The following data were collected:

» Baseline characteristics: demographics, duration of complaints, previous OA-related treatments, concomitant medication.

» Radiographs (at screening): bilateral (posterior-anterior fixed flexion and lateral) knee radiographs were performed and graded using the K&L grading scale by the study physician (GS).

» Questionnaires (at screening, baseline, week 12 and week 24): to estimate knee OA-related symptoms patients were asked to fill out the Dutch version of the Knee injury and Osteoarthritis Outcome Score (KOOS) (Likert-scale version) questionnaire.[25] This questionnaire includes the Western Ontario McMaster Universities (WOMAC) score[26] in its complete and original format (with permission, http://www.koos.nu). WOMAC pain, stiffness and function subscales were presented as normalised scores (0 - 100, where 0 equals no symptoms). To assess quality of life, the Short Form-36 (SF-36)[27] questionnaire was completed by all participants. The SF-36 consists of eight subscales with a score range of 0 - 100, where 100 represents the best possible health situation. The physical (PCS) and mental component summary (MCS) scores were calculated as weighted means of the four physical and four mental subscale scores, respectively (higher scores indicate better health situation).

» Patient global assessment: visual analogue scale-patient global assessment (VAS-PGA), 0 - 100, where 0 equals no symptoms (at screening, baseline, week 12 and week 24).

» (Changes in) OA-related medication use (during all visits).

» Adverse events: during all follow-up visits patients were asked if they experienced any possible adverse events, which were graded for severity. Any adverse event resulting in death, hospitalization, prolongation of hospitalization, or development of a life-threatening or debilitating condition was categorized as a Serious Adverse Event (SAE). Routine laboratory testing (baseline and week 24) included liver and renal function in addition to blood cell counts and vitamin B12 (the latter only at week 24).

» Therapy adherence: pill counts (weeks 12 and 24). Adherence to therapy was defined as use of 80% or more of the total number of study capsules.

## Outcome

The primary endpoint was the difference in proportion of participants in both study groups achieving a clinical response at week 24 defined by the OMERACT-OARSI set of responder criteria,[28] based on the WOMAC pain and function subscale scores and VAS-PGA. The OMERACT-OARSI criteria are defined as: (i) improvement in WOMAC pain (0 - 100) or WOMAC function (0 - 100) 50% or greater with an absolute change of 20 or more; or (ii) improvement of 20% or greater with an absolute change of 10 or more in at least two of the following measures: WOMAC pain, WOMAC function and VAS-PGA. Incomplete questionnaires at baseline were replaced by data from the screening visit (t = -2 weeks) if possible. In addition, incomplete questionnaires at study end (week 24) were replaced by data from the 12-week visit in participants who were still taking study medication at the end of the study (week 24). Participants who ceased study medication prematurely due to adverse events and were lost to follow-up were classified as non-responders. This analysis was done in all subjects who underwent randomisation but also pre-planned in subgroups with and without severe pain (intention to treat analysis).

Secondary endpoints included differences between the two study groups at week 12 and 24 in (change in) the WOMAC subscales, VAS-PGA, MCS and PCS subscales of the SF-36, nature and frequency of adverse events and the (change in) use of OA-related medication at study end.

## Sample size calculation

A difference of 20% response between the placebo and doxycycline group (number needed to treat 5) was considered to be clinically relevant.[28] An OMERACT-OARSI response at 24 weeks in the placebo group of 40% was anticipated.[28] Together with a requested power of 80%, a two-sided significance level of 0.05, an allocation ratio of 1:1 and an expected drop-out at week 24 of 15%, 115 patients were required per treatment arm.

## Statistical analysis

Statistical analyses were performed using STATA/IC 10.1 for Windows. Descriptive statistics were provided by using mean (SD), median (p25-p75) or frequencies/percentages depending on distribution of the data. All analyses were done blinded for treatment allocation.

Analysis of the primary endpoint was carried out using the intention to treat principle and was assessed using the Fisher's exact test. Change scores were calculated by subtracting the baseline scores from the scores at weeks 12 and 24, respectively. Differences between both study groups in change scores of WOMAC subscales, VAS-PGA, PCS and MCS were analyzed using the unpaired t-test. Changes in use of OA-related medication during the trial were categorized in 'more', 'less' and 'unchanged usage' and analysed using the Mann-Whitney U test. The proportions of adverse events in both treatment groups were compared using the Fisher's exact test.

Additional analyses were performed regarding proportion OMERACT-OARSI responders in participants who completed the trial per protocol.

The imputation of missing values of data of patients lost to follow up was considered not appropriate as it was anticipated that loss to follow-up selectively occurred in the

doxycycline group due to adverse effects (missing not at random). Individuals with incomplete data on the primary outcome were classified as non-responders. To calculate change scores (secondary endpoints) only non-missing data was utilized.

## RESULTS

Between April 2008 and April 2010 232 of the 305 patients screened were enrolled and randomised in this study (Figure 1). Subjects in the doxycycline group reported slightly higher scores on WOMAC subscales and concomitant use of analgesics compared with the placebo group. With respect to other possible confounding variables like demographic variables, BMI and K&L grade both study groups were comparable at baseline. Thirty-seven patients had severe pain (Table 1). Among the 232 subjects who were randomised 204 (88%) completed the trial per protocol. Significant more participants in the doxycycline group compared with the placebo group discontinued the study medication prematurely (21 versus 7, p = 0.001). Twelve participants were lost to follow-up (7 doxycycline versus 5 placebo group). Adherence to treatment was satisfactory (i.e. ≥ 80% study capsules taken) in 80% of subjects who were still taking study medication at the final study visit (week 24) and was comparable between both study groups: 80% versus 80% in the doxycycline and placebo group, respectively (p = 1.0).

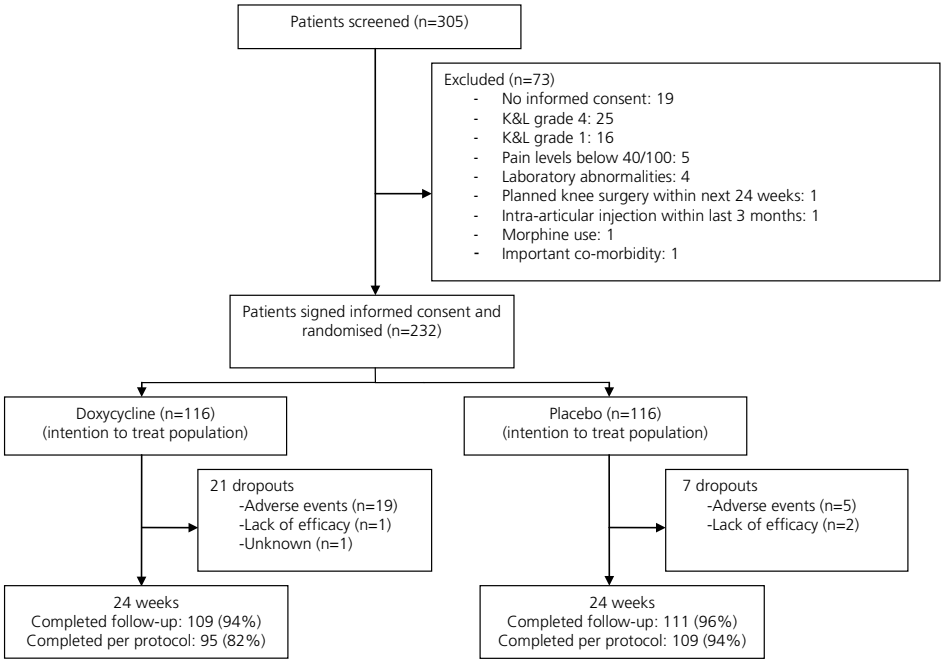


**Figure 1.** Flow diagram
**K&L grade** Kellgren-Lawrence Grading Scale

**Table 1.** Baseline characteristics of patients

| Variable | Total study population (n=232) | Doxycycline (n=116) | Placebo (n=116) |
|---|---|---|---|
| Women, n (%) | 154 (66) | 79 (68) | 75 (65) |
| Age (years), mean (SD) | 59 (9) | 59 (9) | 59 (10) |
| BMI, mean (SD) | 30 (5) | 30 (6) | 30 (5) |
| Duration of knee complaints (years), median (p25-75) | 6 (3-15) | 6 (3-14) | 6 (3-15) |
| K&L-score = 2, number (%) | 151 (65) | 76 (66) | 75 (65) |
| K&L-score = 3, number (%) | 81 (35) | 40 (34) | 41 (35) |
| WOMAC score, mean (SD) | | | |
| Pain | 49 (18) | 52 (19) | 46 (17) |
| Function | 49 (18) | 52 (18) | 47 (17) |
| Stiffness | 56 (21) | 58 (22) | 54 (19) |
| Severe pain, n (%) [1] | 37 (16) | 19 (16) | 18 (16) |
| VAS-PGA, mean (SD) | 52 (25) | 52 (25) | 53 (26) |
| Pain medication use, number (%) [2] | | | |
| Paracetamol | 81 (35) | 50 (43) | 31 (27) |
| NSAID | 95 (41) | 51 (44) | 44 (38) |
| Tramadol | 12 (5) | 4 (3) | 8 (7) |
| None | 85 (37) | 34 (29) | 51 (44) |

[1] WOMAC pain subscale ≥ 60/100. [2] Including on-demand use.
**BMI** body mass index; **K&L-score** Kellgren-Lawrence Grading Scale; **WOMAC** Western Ontario McMaster Universities score; **VAS-PGA** visual analogue scale – patient global assessment; **NSAID** non-steroidal anti-inflammatory drug

## Primary outcome measure

A total of 72 out of 232 (31%) participants met the OMERACT-OARSI criteria for treatment response at the final study visit (week 24). In the doxycycline and placebo group, 31/116 (27%) and 41/116 (35%) met responder criteria at study end, respectively (p = 0.2). In participants with severe pain at week 24, nine responders were identified (2/19 in doxycycline group versus 7/18 in placebo group). Again, no significant difference in the proportion of responders was identified between the doxycycline and placebo group (p= 0.06).

## Secondary outcome measures

In the total study population, a significant improvement of symptoms was observed at week 24. Scores on the WOMAC subscales pain, stiffness, and function, and VAS-PGA decreased from 49 to 41 (n=218), 56 to 50 (n=215), 49 to 42 (n=210) and 52 to 44 (n=200) respectively (all p < 0.001). Regarding quality of life, PCS improved 36 to 38 (p<0.0001), whereas MCS showed no change (53 vs. 54, n=213, p=0.5). However, no differences between the two study groups were found in any measures (Table 2).

### Concomitant use of OA-related medication

Of the 204 participants who were still taking study medication at study end, 153 had unchanged, 23 had increased and 28 had decreased their OA-related medication use at week 24. For the doxycycline and placebo groups these numbers were: 68, 12, 15 and 85, 11, 13, respectively, and showed no significant difference between these groups ($p = 0.9$).

### Safety

During the study, 56% of the participants reported at least one adverse event. Of the 28 subjects who prematurely ceased study medication, 24 did so because of adverse events. Compared to the placebo group, significant more participants who were taking doxycycline ceased treatment because of side effects (19 versus five, $p < 0.01$). Adverse events in both treatment groups reported by more than two subjects are shown in Table 3. The only adverse event which occurred significantly more often in one of the treatment groups was sun sensitivity. The cumulative incidence of upper respiratory tract infection was however somewhat lower in doxycycline treated patients, although this did not reach significance. Development of laboratory abnormalities was rare and did not significantly differ between both treatment groups. In seven subjects (five doxycycline versus two placebo group) low-normal vitamin B12 levels were measured at the end of the study ($p = 0.3$). A total of five SAEs occurred during the trial: one traumatic patella fracture (placebo group), two myocardial infarction (both doxycycline group), one total knee replacement (doxycycline group) and one arthroscopic meniscectomy (placebo group). None of the SAEs were likely attributable to doxycycline, therefore no Suspected Unexpected Serious Adverse Reactions (SUSARs) occurred during the trial.

### Sensitivity analyses

Analysis regarding the proportion of responders in subjects who completed the trial per protocol yielded the same results as the primary analysis. Also, analysis of (non-) response in adherent participants resulted in similar findings.

## DISCUSSION

The findings of the present study indicate that doxycycline is not effective in reducing symptoms in knee OA patients over a 24-week study period, but is associated with increased risk of adverse events. Although previously a possible structure-modifying effect of doxycycline was suggested, this is not accompanied by symptom relief in the short and medium term. Because of the unfavourable risk-benefit ratio, doxycycline should not be used in the management of knee OA.

The lack of effect seen in this study is not caused by insufficient adherence to the medication. Although pill counts showed that ~ 20% of the patient did not reach the target of taking ≥ 80% of study medication, subanalysis in adherent participants yielded the same findings. Although varus malalignment may have negated the symptom-modifying

**Table 2.** Secondary outcomes: improvements and differences between study groups

| | Doxycycline | | Placebo | | |
|---|---|---|---|---|---|
| **Outcome measure** | **n** | **Mean (95% CI)** | **n** | **Mean (95% CI)** | **Difference (95 % CI)** |
| *WOMAC pain* | | | | | |
| Baseline [SD] | 116 | 52 [19] | 115 | 46 [17] | |
| Δ Week 12 - Baseline | 107 | -8 (-4 to -11) | 110 | -7 (-4 to -11) | 0 (-5 to 5) |
| Δ Week 24 - Baseline | 108 | -8 (-5 to -12) | 110 | -8 (-3 to -12) | 0 (-6 to 5) |
| *WOMAC stiffness* | | | | | |
| Baseline [SD] | 115 | 58 [22] | 113 | 54 [19] | |
| Δ Week 12 - Baseline | 106 | -7 (-3 to -11) | 110 | -9 (-5 to -13) | 2 (-4 to 7) |
| Δ Week 24 - Baseline | 108 | -5 (-1 to -8) | 107 | -7 (-3 to -12) | 3 (-3 to 8) |
| *WOMAC function* | | | | | |
| Baseline [SD] | 112 | 52 [18] | 115 | 47 [17] | |
| Δ Week 12 - Baseline | 104 | -7 (-4 to -10) | 109 | -7 (-3 to -10) | -1 (-5 to 4) |
| Δ Week 24 - Baseline | 103 | -8 (-4 to -11) | 107 | -7 (-3 to -10) | -1 (-6 to 4) |
| *VAS-PGA* | | | | | |
| Baseline [SD] | 112 | 52 [25] | 115 | 53 [26] | |
| Δ Week 12 - Baseline | 100 | -7 (-1 to -13) | 106 | -9 (-3 to -15) | 1 (-7 to 10) |
| Δ Week 24 - Baseline | 95 | -7 (-1 to -13) | 105 | -10 (-3 to -17) | 3 (-6 to 12) |
| *PCS (possible range 4 – 71)** | | | | | |
| Baseline [SD] | 114 | 36 [8] | 114 | 36 [7] | |
| Δ Week 12 - Baseline** | 104 | 2 (0 to 3) | 109 | 3 (1-4) | -1 (-3 to 1) |
| Δ Week 24 - Baseline** | 105 | 2 (1 to 3) | 108 | 2 (1 to 4) | 0 (-2 to 3) |
| *MCS (possible range 2 – 74)** | | | | | |
| Baseline [SD] | 114 | 52 [11] | 114 | 54 [11] | |
| Δ Week 12 - Baseline** | 104 | 1 (-1 to 2) | 109 | -1 (-3 to 1) | 2 (0 to 4) |
| Δ Week 24 - Baseline** | 105 | 1 (-1 to 2) | 108 | 0 (-1 to 2) | 0 (-2 to 3) |

Negative signs indicate improvement within groups (unless stated otherwise) or improvement in favour of doxycycline (in case of differences in change between groups). Scores are normalised (0-100; 0 = no symptoms) unless stated otherwise. * Norm-based scores, higher scores indicate better health, individual scores in the 45-55 range indicate average health. ** Negative signs indicate deterioration within groups or improvement in favour of placebo (in case of differences in change between groups).**WOMAC** Western Ontario McMaster Universities, **PCS** Physical Component Score, **MCS** Mental Component Score.

**Table 3.** Adverse events in both study groups

| Adverse event | Total study population (n=232), n (%)[1] | Doxycycline (n=116), n (%) | Placebo (n=116), n (%) | P | Doxycycline | | Placebo | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Led to temporarily discontinuation, n[2] | Led to permanent discontinuation, n | Led to temporarily discontinuation, n | Led to permanent discontinuation, n |
| Sun sensitivity | 38 (16) | 35 (30) | 3 (3) | <0.001 | 6 | 9 | 0 | 1 |
| Diarrhea | 25 (11) | 15 (13) | 10 (9) | 0.40 | 1 | 5 | 0 | 1 |
| Abdominal discomfort | 16 (7) | 6 (5) | 10 (9) | 0.44 | 0 | 4 | 0 | 1 |
| Erythema | 12 (5) | 8 (7) | 4 (3) | 0.38 | 1 | 2 | 0 | 1 |
| Nausea | 10 (4) | 5 (4) | 5 (4) | 1.0 | 0 | 1 | 0 | 1 |
| Upper respiratory tract infection | 9 (4) | 2 (2) | 7 (6) | 0.17 | 1 | 0 | 1 | 0 |
| Arthralgia/ myalgia | 8 (3) | 4 (3) | 4 (3) | 1.0 | 0 | 2 | 0 | 0 |
| Headache | 7 (3) | 4 (3) | 3 (3) | 1.0 | 0 | 0 | 1 | 0 |
| Edema | 6 (3) | 3 (3) | 3 (3) | 1.0 | 0 | 0 | 0 | 0 |
| Constipation | 6 (3) | 4 (3) | 2 (2) | 0.68 | 1 | 1 | 0 | 0 |
| Mycosis | 5 (2) | 4 (3) | 1 (1) | 0.37 | 1 | 1 | 0 | 0 |
| Other | 26 (11) | 10 (9) | 16 (14) | 0.30 | 2 | 2 | 1 | 2 |

[1] Subjects could have reported more than one adverse event. [2] Subjects could have ceased treatment because of more than one adverse event.

effect of doxycycline as reported for the structure-modifying effect of doxycycline,[29] this seems very unlikely as major malalignment was one of the exclusion criteria.

Generalisability seems to be fair as the study group is comparable with other cohorts of knee OA consisting mainly of middle-aged obese women.[30;31] In this study a relatively low frequency of subjects experienced severe knee pain (16%). This is in contrast to other more symptomatic knee OA cohort studies, like for example the secondary care CONTROL-PRO cohort in which 54% of knee OA patients experience severe pain.[32] However, stratified analyses in patients with severe pain did not show any trend for a symptom-reducing effect of doxycycline. Also, results of our study possibly cannot be extrapolated to knee OA patients with low or high radiographic K&L scores (i.e. $\leq 1$ or $> 3$). It could be possible that we included participants with slightly less extensive radiographic OA compared to other studies, because radiographs obtained in flexion view may have a higher sensitivity for OA-related radiographic changes compared to conventional AP views.[33] However, this does not challenge the validity of the present study as it does not compromises the external validity, because in both K&L groups a lack of response was observed indicating absence of effect modification.

To our knowledge, up to now no other studies have evaluated the effects of doxycycline on symptoms caused by OA. As mentioned earlier, the only study of doxycycline in human knee OA[13] indicated that this agent retards radiographic progression of knee OA, although the primary goal of the study – reduction of progression of less extensive knee OA – was not met. A trend to pain reduction was also seen, possibly reflecting the anti-inflammatory effect of tetracyclines as studied for minocycline in RA.[34]

Although doxycycline (as a metalloproteinase inhibitor) does not seem to be a symptom modifier in the short and medium term in knee OA patients with moderate pain, this agent could still have potential structure-modifying effects. However, use of doxycycline for a longer period has some drawbacks regarding to side effects (mainly sun sensitivity) and possibly development of anti-microbacterial resistance. Therefore, effort has been made to develop synthetic metalloproteinase inhibitors,[35;36] though until now without a favourable risk-benefit ratio.

Future research should give insight in the structure-modifying properties of inhibition of metalloproteinases in human OA. Regarding symptom modifying in OA, improvement of strategies of existing treatment modalities[37] or development of new classes of analgesics[38] will probably result in better outcomes in patients with symptomatic OA.

In conclusion, present study showed that twice daily doxycycline during 24 weeks did not have any effect on symptoms in knee OA patients, compared to placebo. Therefore doxycycline should not be applied as symptom modifier in knee OA.

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# 4

# EVIDENCE-BASED TAILORED CONSERVATIVE TREATMENT OF KNEE AND HIP OSTEOARTHRITIS: BETWEEN KNOWING AND DOING

# ABSTRACT

**Objectives** Insufficient data are available on the efficacy of combined conservative interventions recommended by treatment guidelines for knee and/or hip osteoarthritis (OA). The aims of this observational cohort study were 1) to estimate the results of an evidence-based 12-week tailored multimodal conservative treatment protocol for patients with knee and/or hip OA and 2) to identify predictors for response.

**Methods** After obtaining data on previous OA-related interventions, multimodal treatment was offered to patients with knee and/or hip OA at a specialised outpatient clinic. Treatment with analgesics was tailored using a numeric rating scale (NRS) for pain, aiming for NRS ≤ 4. The following outcome measures were assessed: 1) the proportion of patients fulfilling OMERACT-OARSI responder criteria and 2) the proportion of patients with NRS pain ≤ 4 after 12 weeks.

**Results** A total of 183 out of 299 patients was included. OMERACT-OARSI responder criteria were fulfilled at 12 weeks in 47% of patients; 39% reached a NRS pain ≤ 4. The only independent predictor for response was the number of previously used non-steroidal anti-inflammatory drugs (NSAIDs). The majority of patients had not been exposed adequately to conservative treatment modalities for knee and/or hip OA in the past (81%).

**Conclusion** Evidence-based multimodal conservative treatment using a standardised protocol for knee and/or hip OA is feasible and successful in 47% of patients. In general, response could not be predicted. Basic first-line recommended conservative treatment options have not been adequately utilized prior to referral to secondary care in the vast majority of patients.



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# INTRODUCTION

Recommendations in several evidence-based guidelines for knee and hip osteoarthritis (OA) consist of combinations of non-pharmacological and pharmacological interventions like information about OA, the importance of change in lifestyle, weight reduction, referral to a physical therapist for aerobic or strength improvement, the use of analgesics like paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs), and steroid injection therapy.[1-13]

Although individual symptomatic interventions have been shown to be effective, insufficient data is available on the feasibility and efficacy of a combination of these interventions and possible predictors for response. Only one study investigated recommendations in a randomised controlled design, but unlike present study, prescription of analgesics was not standardised.[14]

Therefore, based on the aforementioned guidelines, a 12-week standardised treatment protocol was developed including education, advice about weight loss and lifestyle measures, numeric rating scale (NRS)-tailored use of analgesics, and referral to a physical therapist. The protocol was implemented at a specialised outpatient clinic for conservative treatment of knee and hip OA. In addition, consenting patients were included in an observational cohort study: Cohort Of Non-invasively TReated Osteoarthritis of Lower extremities - Pain, function and Radiological Outcome (CONTROL-PRO) study.

The aims of this study were 1) to estimate the results of an evidence-based 12-week tailored multimodal conservative treatment protocol for patients with knee and/or hip OA and 2) to identify predictors for response.



# PATIENTS AND METHODS

## Design

An observational cohort study to investigate an evidence-based standardised conservative treatment protocol of knee and/or hip OA was performed.

## Patients

All patients referred to the Rheumatology specialised outpatient clinic ('knie/heup artrose poli', knee/hip OA clinic) of the Sint Maartenskliniek, Nijmegen, The Netherlands with knee and/or hip OA fulfilling the clinical American College of Rheumatology (ACR) criteria were considered for inclusion in this observational cohort study.[15;16] For knee OA the following criteria were used: knee pain (> 15 days of last month) plus at least three of the following: age > 50 years, morning stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement or no palpable warmth. For hip OA the following criteria were used: hip pain (> 15 days of last month) plus internal rotation of the hip < 15° and erythrocyte sedimentation rate (ESR) ≤ 45 mm/hr or hip pain (> 15 days of last month) plus internal rotation of the hip ≥ 15° and painful internal rotation of the hip and morning stiffness ≤ 60 minutes and age > 50 years.

The exclusion criteria were: pain in the knee or hip on a numeric rating scale (NRS, 0-10) of 4 or lower, inflammatory rheumatic diseases or deposition diseases possibly leading to inflammatory arthritis or secondary OA, severe orthopaedic abnormalities, co-morbidity exceeding the complaints of limitations of knee or hip OA, cognitive or sensomotor problems interfering with the use of questionnaires and planned orthopaedic procedures within the next 12 weeks. Allowed were calcium pyrophosphate deposition disease (CPPD; excluding the phenotypes pseudogout and polyarthritis) and previous meniscus problems.

Patients were asked at the first visit whether they would be willing to participate in the observational study (CONTROL-PRO), and if so informed consent was obtained by the treating physician. In patients not fulfilling inclusion and exclusion criteria or who did not consent, treatment was performed unaltered according to the treatment protocol.

## Specialised knee/hip OA outpatient clinic treatment protocol

All patients that were treated at the specialised knee/hip OA outpatient clinic received standardised evidence-based tailored conservative treatment in a stepped-care format as usual care for 12 weeks. This stepped-care model is based on a recently online published Dutch multidisciplinary guideline for diagnosis and treatment of knee and hip OA and has been proposed by a consensus panel of leading experts in the field of OA in The Netherlands.[17;18]

The goal of the intervention was to reduce the level of pain on a NRS to 4 or lower. Visits were planned at week 0 and 12 at the outpatient clinic and at week 4 and 8 by telephone and managed by a research physician (GS), a physician assistant (VS) or a nurse practitioner. When NRS pain remained higher than 4 and patients had taken the prescribed medication for at least two weeks adequately, an analgesic outlined in the next step of the stepped-care model was offered.

The first step of the treatment protocol consisted of education, life style advice concerning physical activity, weight loss advices in patients with a body mass index (BMI) of 28 or higher (goal: 5% weight loss in 12 weeks), referral for first-line physical therapy (i.e. prescription for both aerobic and strengthening exercises according to the graded activity principle), and treatment with paracetamol in a fixed dose of thrice a day 1000 mg (in case of no recent use for knee and/or hip complaints) (Figure 1). In the second step, if necessary and no earlier than after 4 weeks, a NSAID was added. The choice for a specific drug was based on previous exposure to specific NSAIDs. The preferential agent was naproxen, twice a day 500 mg. The third step consisted of substitution of naproxen for meloxicam once a day 15 mg or ibuprofen thrice a day 600 mg. The fourth step included the substitution of the NSAID for tramadol (thrice a day 50 mg).

## Baseline data and data on previous treatments

Baseline data were collected on demographic and disease-related characteristics using a standardised interview and physical examination. Data on previously used treatment modalities concerning knee and/or hip OA were obtained using a standardised interview consisting of a checklist with all common prescribed analgesics (only analgesics prescribed

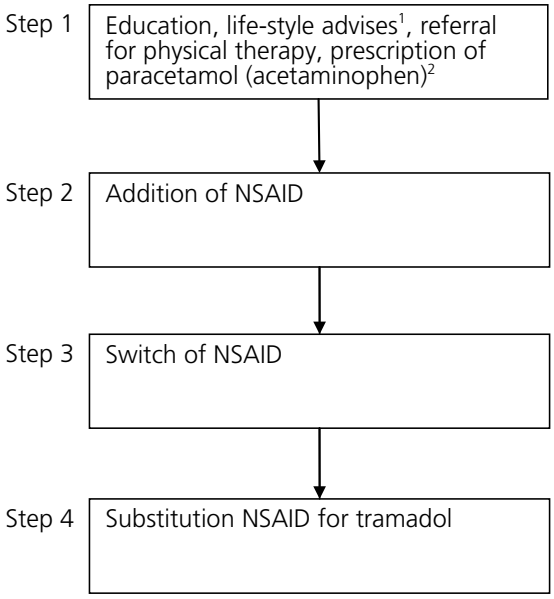


**Figure 1.** Diagram of treatment protocol. When NRS remained > 4 after 4 weeks, the next step was offered. [1]Including weight loss if BMI ≥ 28 (goal: 5% reduction of weight in 12 weeks). [2]In case of recent use of paracetamol: direct start of NSAID at first visit (step 2). **NSAID** non-steroidal anti-inflammatory drug; **BMI** body mass index; **NRS** numeric rating scale (0-10)



for at least 14 consecutive days were counted; no exact dosages were required), intra-articular injections, supplements (i.e. glucosamine and chondroitin) and physical therapy (minimum attendance to two sessions was required). In addition, every referred patient was asked to bring a list from the pharmacist or general practitioner with past prescribed medication to the first visit at the outpatient clinic.

## Radiographs

Bilateral (posterior-anterior (PA) fixed flexion and lateral) knee and pelvic radiographs were performed in all participants.[19] Scoring of radiographs was done using Kellgren-Lawrence Grading Scale (K&L-score) by an experienced rheumatologist and a research physician (GS).[20]

## Numeric Rating Scales and questionnaires

At each visit (by telephone and at the outpatient clinic) NRS on pain and patient global assessment (PGA) (0-10) were administrated.

## Knee/Hip injury and Osteoarthritis Outcome Score (KOOS/HOOS) and Western Ontario McMaster Universities (WOMAC) score

At baseline and at 12 weeks, patients were asked to fill out the KOOS or HOOS (Likert-scale version) questionnaire. These questionnaires include the WOMAC OA index in its complete and original format (with permission, http://www.koos.nu). WOMAC pain, stiffness and function subscales were calculated at baseline and after 12 weeks and presented as normalised scores (0-100, where 0 equals no symptoms).

### Outcome

The outcome measures included the proportion of patients after 12 weeks fulfilling OMERACT-OARSI criteria for response[21] and the proportion of patients after 12 weeks with NRS pain ≤ 4.The OMERACT-OARSI criteria are defined as: 1) improvement in NRS pain (0-10) or WOMAC function (0-100) ≥ 50% with an absolute change ≥ 2 (NRS pain) or ≥ 20 (WOMAC function); or 2) improvement of ≥ 20 % with an absolute change ≥ 1 (NRS pain) or ≥ 10 (WOMAC function) in at least two of the following measures: NRS pain, WOMAC function and NRS PGA.

### Statistics

Since the study was observational, no formal null-hypothesis could be formulated. However, an exploratory sample size calculation was made as follows: to be able to estimate an OMERACT-OARSI response proportion of 0.4, with a confidence interval of < 0.1, an alpha of 0.05 and a power of 0.8, a total of 154 patients were necessary.

Patients with/without OMERACT-OARSI response after 12 weeks treatment were compared using the $\chi^2$-test for nominal variables and the independent *t*-test/Wilcoxon rank-sum test for continuous variables (depending on normality). To predict an OMERACT-OARSI response, a prediction model was build. Predefined possible predictive variables (at baseline) were: NRS pain, NRS PGA, WOMAC function subscale, age, BMI, K&L score, number of previously used NSAIDs, previous use of paracetamol, surgical procedures for knee or hip OA and duration of knee or hip complaints. Finally, past use of key elements of the treatment guideline (defined as at least: paracetamol ≥ twice a day 1000 mg, at least one NSAID and physical therapy for knee and/or hip OA) was predefined as possible predictor. These variables were univariately tested first and, when an association with OMERACT-OARSI response was found, entered in a multivariate logistic regression analysis.

### Ethical considerations

The standardised treatment protocol was performed as routine clinical care in the Sint Maartenskliniek. The local Medical Research Ethics Committee (MREC), region Arnhem-Nijmegen (the Netherlands) approved the study design of CONTROL-PRO (local study number 2009/095).

## RESULTS

Between July 2007 and July 2009, 299 patients were treated according to the aforementioned standardised treatment protocol (Figure 2). A total of 231 patients fulfilled inclusion and exclusion criteria, and finally sufficient follow-up data were available to calculate response status after 12 weeks from 183 patients. The main reasons for insufficient data were lost of follow-up and incomplete questionnaires. Baseline characteristics are depicted in Table 1. There were no significant differences at baseline between patients with and without sufficient 12-week follow-up data (except a slightly higher NRS pain in patients without or insufficient follow-up data, 6.7 vs. 7.1 p=0.04).

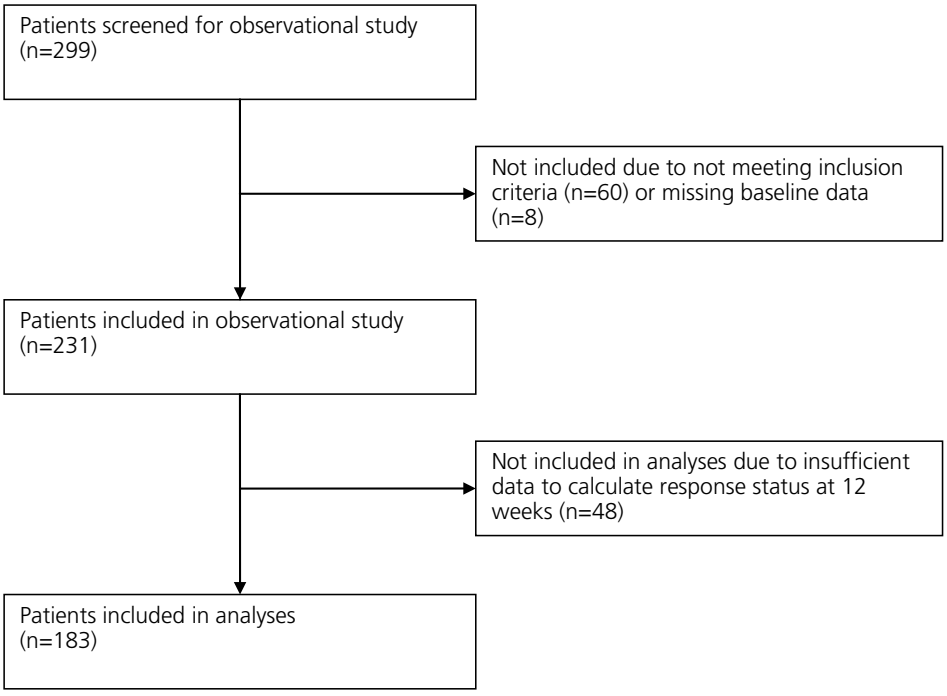


**Figure 2.** Study flow diagram.

The vast majority of patients has not been exposed adequately to conservative treatment modalities for knee and/or hip OA in the past (81%). After 4, 8 and 12 weeks 21%, 30% and 39% of patients, respectively, had a NRS pain ≤ 4. OMERACT-OARSI response criteria were fulfilled in 86 (47%) patients after 12 weeks. Significant improvements in NRS pain, NRS PGA and two of three WOMAC subscales were measured at 12 weeks (Table 2). In the univariate analysis, NRS pain at baseline and number of NSAIDs used for OA were significantly associated with an OMERACT-OARSI response, with only the latter remaining as independent predictor for OMERACT-OARSI response after 12 weeks in the multivariate analyses (OR 0.77, 95% CI 0.60-0.99). Other variables were not associated with a treatment response (Table 3).

## DISCUSSION

Our study shows that standardised tailored use of simple conservative treatment as usual care results in reaching of an OMERACT-OARSI response being reduced in 47% of patients with knee and/or hip OA. Strong independent predictors for short-term response, however, could not be identified except a low number of previously used NSAIDs for knee and/or hip OA. In addition, basic first-line recommended conservative treatment options had not been used adequately prior to referral to secondary care in the large majority of patients.

**Table 1.** Baseline characteristics of patients (n=183)

| **Variable** | |
|---|---|
| Women, n (%) | 128 (70) |
| Age (years), mean (SD) | 56 (10) |
| BMI, median (p25-75) | 29 (25-32) |
| Knee OA, number (%) | 153 (84) |
| Duration of knee/hip complaints (years), median (p25-75) | 4 (2-9) |
| Disease duration (years), median (p25-75) | 1 (0-3) |
| K&L-score ≥ 2, number (%) | 109 (60) |
| Past treatment, number (%) | |
| Key elements of guidelines utilized[1] | 35 (19) |
| Analgesics | |
| None | 14 (8) |
| Paracetamol (acetaminophen) | 138 (75) |
| Paracetamol in adequate dose[2] | 66 (36) |
| One or more NSAID | 149 (81) |
| Opioids[3] | 38 (21) |
| Supplements[4] | 85 (47) |
| Physical therapy | 118 (64) |
| Past surgical treatments for knee OA, number (%) | |
| One or more arthroscopies[5] | 86/153 (56) |
| Open procedures[6] | 26/153 (17) |
| Past surgical treatments for hip OA, number (%) | |
| One or more arthroscopies | 0/30 |
| Open procedures | 4/30 (13) |
| Past knee or hip trauma, number[7] (%) | 23 (13) |

[1]Defined as at least: paracetamol ≥ twice a day 1000 mg (for at least 14 consecutive days), at least one NSAID (for at least 14 consecutive days) and physical therapy (at least two sessions) for knee and/or hip OA; [2]Adequate dose: 2-4 times 1000mg/day during at least 14 consecutive days; [3]Including tramadol; [4]Glucosamine and chondroitin; [5]Including partial meniscectomy; [6]Including joint prosthesis; [7]e.g. damage to ligaments. **BMI** body mass index; **OA** osteoarthritis; **K&L-score** Kellgren-Lawrence Grading Scale; **NSAID** non-steroidal anti-inflammatory drug

Therefore, in our opinion, our findings strongly suggest that all symptomatic knee and hip OA patients - regardless of demographic, disease-related characteristic or previous treatments - should be offered conservative treatment according to existing guidelines first, before (partial) joint replacement is considered.

The internal validity of our study seems adequate, illustrated by ample precision. However, the uncontrolled design should urge caution regarding conclusions to be

**Table 2.** Results after 12 weeks

| | Baseline | Week 12 | Change | 95% CI |
|---|---|---|---|---|
| Responder[1] (%) | | 47 | | 40 to 54 |
| NRS pain (0-10) (SD) | 6.7 (1) | 5.3 (2) | 1.4 (2) | -1 to -2 |
| NRS PGA (0-10) (SD) | 6.9 (2) | 5.6 (2) | 1.3 (2) | -0.9 to -2 |
| WOMAC, mean (SD)[2] | | | | |
| pain | 57 (19) | 52 (23) | -5.1 (19) | -2 to -8 |
| stiffness | 62 (20) | 58 (23) | -3.8 (23) | 0 to -8 |
| function | 58 (19) | 52 (23) | -5.6 (19) | -3 to -8 |
| 5% weight loss if BMI >28 at baseline (%), n=72 | | 14 | | 6 to 22 |

[1]According to OMERACT-OARSI criteria [2] Scores are normalised (0 –100; 0 = no symptoms). **NRS** numeric rating scale; **WOMAC** Western Ontario McMaster Universities score; **BMI** body mass index.



drawn about the effect of the intervention. Improvement of symptoms could also, at least partly, be explained by regression to the mean (natural history) or expectation bias (placebo effect). However, spontaneous regression of complaints seems to be an unlikely explanation because the waiting time for our outpatient clinic was approximately two to three months before inclusion. Moreover, all interventions integrated in the treatment protocol have shown symptomatic efficacy in randomised controlled trials (RCTs).[10;22;22-24] Therefore, it seems unlikely that regression to the mean would be the major contributing cause for the perceived effect of the intervention.

Adherence is known to be a potent effect modifier in clinical practice. Since adherence was not measured routinely in this study, non-adherence to prescribed treatment modalities could have resulted in lower response percentages. Nevertheless, this pragmatic study was intended to estimate the results of the treatment protocol in daily clinical practice, thus including the effect of non-adherence. Therefore an intention-to-treat analysis was preferable over a per-protocol analysis (which perhaps would have resulted in higher response rates).

Generalizability of the results of our study seems limited to symptomatic knee and hip OA patients in secondary care. In this regard, our cohort is comparable with other cohorts, consisting mainly of obese women with knee OA.[25;26] Level of pain and BMI, however, are higher and patients were younger, possibly reflecting some selection as these patients are not ideal candidates for joint replacement after failing conservative treatment in primary care. Therefore, they are more likely to be referred for secondary care for conservative treatment. Moreover, only patients with a NRS of 4 or higher were included in this study. Although some additional selection could have arisen from competitive inclusion with a RCT regarding knee OA with mild or moderate radiographic degenerative changes during the inclusion period, K&L scores seem to be evenly distributed.

In the present study, only two predictors for treatment response were identified (with only one remaining significant after multivariate analysis), but several possible predictors

**Table 3.** Results of univariate logistic regression analysis of possible predictors (at baseline) for OMERACT-OARSI response at 12 weeks

| Variable | OR | 95% CI |
|---|---|---|
| Gender (male) | 0.60 | 0.31-1.14 |
| Age | 1.01 | 0.99-1.05 |
| Index joint (knee) | 0.71 | 0.32-1.58 |
| NRS pain | 0.77 | 0.60-0.99 |
| NRS PGA | 0.90 | 0.77-1.06 |
| WOMAC function | 0.99 | 0.98-1.01 |
| BMI | 1.03 | 0.98-1.09 |
| Duration of complaints, in years | 1.01 | 0.98-1.05 |
| K&L-score | 1.09 | 0.85-1.40 |
| Past knee or hip trauma[1] | 0.69 | 0.28-1.69 |
| Key elements of guidelines utilized[2] | 0.70 | 0.33-1.49 |
| Past physical therapy for knee or hip OA | 0.59 | 0.32-1.09 |
| Number of NSAIDs used | 0.76 | 0.63-0.93 |
| Adequate use of paracetamol[3] | 1.10 | 0.60-2.01 |
| Past arthroscopies (knee OA)[4] | 0.95 | 0.71-1.28 |
| Past open surgical procedures[5] | 0.64 | 0.72-3.50 |

[1]e.g. damage to ligaments; [2]Defined as at least: paracetamol ≥ twice a day 1000 mg (for at least 14 consecutive days), at least one NSAID (for at least 14 consecutive days) and physical therapy (at least two sessions) for knee and/or hip OA; [3]Adequate dose: 2-4 times 1000 mg/day during at least 14 consecutive days; [4]Including partial meniscectomy
[5]Including joint prosthesis. **OR** odds ratio; **CI** confidence interval; **NRS** numeric rating scale; **PGA** patient global assessment; **WOMAC** Western Ontario McMaster Universities score; **BMI** body mass index; **K&L-score** Kellgren-Lawrence Grading Scale; **NSAIDs** non-steroidal anti-inflammatory drugs

that currently have not been investigated should be subject of investigation in future research. Among variables to be considered are serum/urine biomarkers related to inflammation or cartilage breakdown, specific features on (functional) imaging techniques or psychological factors.

Although the finding that basic treatment modalities including paracetamol and physical therapy have not been adequately utilized prior to referral to secondary care in a substantial number of patients has been reported earlier, this is striking, bearing in mind that around 80% of our patients were referred to the knee/hip OA outpatient clinic by orthopaedic surgeons (data not shown). In most of these cases, patients were referred to secondary care for surgical treatment by primary healthcare workers, without offering adequate conservative treatment first. This finding is in concordance with studies on adherence to guidelines for knee OA.[27;28] Notably, the point-estimates regarding past

treatment modalities could be influenced by recall bias. However, recall bias might not be a confounder for the relation between past treatment (as a predictor) and OMERACT-OARSI response as it is unlikely that patients who do not recall past treatments adequately should have a different chance to respond to the offered treatment protocol.

The advice to reduce weight in case of obesity (with the goal being 5% reduction of body weight) was accomplished in 14% after 12 weeks. Although this number seems rather low, it is encouraging that this was solely reached by the advice to lose weight and referral for physical therapy. Moreover, weight reduction in combination with exercise is associated with improvements of self-reported measures of daily functioning and pain in obese older patients with knee OA.[12] Nevertheless, more tailored approaches directed to weight reduction would be helpful, as the majority of obese patients in the present study did not lose weight.

A few questions arose that should be answered in future research. Although a short-term response rate of 47% was reached with the described approach, the sustainability of these effects is so far unknown. In addition, the present results lead to the need to identify factors (e.g. kinesiophobia[29]) associated with no or minimal weight reduction, to be able to tailor approaches against obesity. Other important questions to be answered consider the ideal strategy of analgesic treatment in knee and/or hip OA. Although these agents are recommended in several guidelines, it is unknown whether NSAIDs should be added to paracetamol in the case of lack of effect, or that paracetamol should be substituted for a NSAID. Also, it is unknown whether the chance of response to a second or third NSAID is lower compared to the first NSAID, and whether (partial) opiates might be the better option. Furthermore, the optimal timing of and patient selection for injection therapy is thus far unidentified. Finally, assessing and improving adherence to therapy could be important approaches in the conservative treatment of knee and/or hip OA.

In conclusion, evidence-based tailored conservative treatment using a standardised protocol was feasible and successful in 47% of patients, but response to treatment could largely not be predicted. Basic first-line recommended conservative treatment options have not been adequately utilized prior to referral to secondary care in the large majority of patients. Healthcare workers should therefore be encouraged to offer adequate conservative treatment, as recommended in several evidence-based treatment guidelines, to all patients with knee and/or hip OA.

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# 5

# TREATMENT OUTCOMES OF A NUMERIC RATING SCALE-GUIDED PHARMACOLOGICAL PAIN MANAGEMENT STRATEGY IN SYMPTOMATIC KNEE AND HIP OSTEOARTHRITIS IN DAILY CLINICAL PRACTICE

# ABSTRACT

**Objectives** To describe the results of a numeric rating scale (NRS)-guided pharmacological pain management strategy in symptomatic knee and/or hip osteoarthritis (OA) in daily clinical practice.

**Methods** In this observational cohort study, standardised conservative treatment was offered to patients with symptomatic knee and/or hip OA. Treatment with analgesics was tailored using a NRS for pain, aiming for NRS ≤ 4. The first step in pharmacological treatment was paracetamol (acetaminophen) in case of no recent use in adequate dose, after 4 weeks followed by NSAID 1 and subsequently after 4 weeks by a switch to NSAID 2 in case of treatment failure. Predictors for response to treatment were identified. Moreover, reasons for non-adherence to the protocol were collected.

**Results** 347 patients were included. The proportion of patients that reached a response (NRS ≤ 4) after paracetamol, NSAID 1 and NSAID 2 was 25% (59 / 234), 16% (31 / 190) and 11% (10 / 87), respectively. Non-adherence to the protocol occurred in 46% of cases when switch of the analgesic was advised, mainly due to unwillingness of patients to take a (new) NSAID. Identified predictors for response to analgesics included higher age, lower patient global assessment, less stiffness and more radiographic severity.

**Conclusion** Adequate use of paracetamol and switching to a NSAID after failing paracetamol resulted in moderate treatment response percentages, whereas the result of the second NSAID was disappointing in patients with advanced knee and/or hip OA. Predictors for response included patient and disease related factors. A substantial part of patients with NRS > 4 were unwilling to change their analgesics.



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Submitted

# INTRODUCTION

Recommendations in several evidence-based guidelines for knee and hip osteoarthritis (OA) consist of combinations of non-pharmacological, e.g. education, physical therapy and weight reduction, and pharmacological interventions.[1-4] Because Disease Modifying Osteoarthritic Drugs (DMOADs) are not yet available, the most important pharmacological intervention is treatment with analgesics, principally using paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAIDs) and (partial) opioids. In aforementioned guidelines, paracetamol is generally recommended as analgesic of first choice in the treatment of pain and disability related to knee or hip OA, as NSAIDs are associated with more side effects like gastrointestinal and cardiovascular complications.[5;6]

The efficacy of paracetamol and NSAIDs in knee and hip OA has been demonstrated in several randomised controlled trials (RCTs).[7;8] Although most studies on NSAIDs suggest more OA-related pain reduction than paracetamol,[9;10] a few head-to-head studies indicated that the superiority of NSAIDs over paracetamol is questionable.[11;12] Moreover, the clinical important questions whether prescription of a NSAID after failure of paracetamol and switch to another NSAID after an insufficient response to the first NSAID is warranted, have never been subject to research. Finally, because there is a large variation in the response to pain medication,[13;14] it could be of value to identify predictors for response.

In our centre, based on the aforementioned guidelines and almost similar to the recently developed treatment strategy on knee and hip OA in The Netherlands,[15] a 12-week standardised treatment protocol was developed consisting of a numeric rating scale (NRS)-guided pain management strategy (paracetamol, NSAIDs and eventually tramadol), in addition to education, advice about weight loss and lifestyle measures, and referral to a physical therapist. The protocol was implemented at a specialised outpatient clinic for conservative treatment of knee and hip OA.[16]

The aims of present study were 1) to describe the results of a NRS-guided pain management strategy in symptomatic knee and hip osteoarthritis (OA) in daily clinical practice and 2) to identify predictors for response in daily clinical practice in symptomatic secondary care knee and/or hip OA.

# PATIENTS AND METHODS

## Patients

All patients referred to the Rheumatology specialised outpatient clinic ('knie/heup artrose poli', knee/hip OA clinic) of the Sint Maartenskliniek with knee and/or hip OA fulfilling the clinical American College of Rheumatology (ACR) criteria[17;18] were considered for inclusion in this observational cohort study. For knee OA the following criteria were used: knee pain (> 15 days of last month) plus at least three of the following: age > 50 years, morning stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement or no palpable warmth. For hip OA the following criteria were used: hip pain (> 15 days of last month) plus internal rotation of the hip < 15° and erythrocyte sedimentation rate (ESR) ≤ 45 mm/

hr or hip pain (> 15 days of last month) plus internal rotation of the hip ≥ 15° and painful internal rotation of the hip and morning stiffness ≤ 60 minutes and age > 50 years.

The exclusion criteria were: pain in the knee or hip on a numeric rating scale (NRS, 0-10) of ≤ 4, inflammatory rheumatic diseases or deposition diseases possibly leading to inflammatory arthritis or secondary OA, co-morbidity exceeding the complaints of limitations of knee or hip OA, cognitive or sensomotor problems interfering with the use of questionnaires and planned orthopaedic procedures within the next 12 weeks. Allowed were calcium pyrophosphate deposition disease (CPPD) (excluding the phenotypes pseudogout and polyarthritis) and previous meniscus problems.

All patients were asked to participate in the CONTROL-PRO study,[16] an observational cohort study tightly integrated with the specialised outpatient clinic.

## Specialised knee/hip OA outpatient clinic treatment protocol

All patients, treated at the specialised knee/hip OA outpatient clinic, received standardised evidence-based tailored conservative treatment in a stepped-care format as usual care for 12 weeks. This stepped-care model is based on an online published Dutch multidisciplinary guideline for diagnosis and treatment of knee and hip OA and has been proposed by a consensus panel of leading experts in the field of OA in The Netherlands.[15]

The goal of the intervention was to reduce the level of pain on a NRS to ≤ 4. Visits were planned at week 0 and 12 at the outpatient clinic and at week 4 and 8 by telephone and managed by the research physician (GS), a physician assistant or a nurse practitioner. When NRS pain remained higher than 4 and patients had taken the prescribed medication for at least two weeks adequately, the next step of the stepped-care model was offered (see below).

The first step of the treatment protocol consisted of education, life style advice concerning physical activity, weight loss advices in patients with a body mass index (BMI) of ≥ 28 (goal: 5% weight loss in 12 weeks), referral for first-line physical therapy (i.e. prescription for both aerobic and strengthening exercises according to the graded activity principle), and treatment with paracetamol in a fixed dose of thrice a day 1000 mg, in case of no recent use in adequate dose (2-4 times 1000 mg/day during at least 14 consecutive days) for knee and/or hip complaints. (In case of recent use of paracetamol, treatment with a NSAID was initiated in the first step). In the second step, if necessary and no earlier than after 4 weeks, a NSAID (NSAID 1) was advised. The choice for a specific drug was based on previous exposure to specific NSAIDs. The preferential agent was naproxen, twice a day 500 mg. During the observation period two different polices were applied; before August 2009 paracetamol was continued when NSAID 1 was initiated (n = 44), whereas after August 2009 paracetamol was discontinued if the first NSAID was prescribed (n = 33). The third step consisted of substitution of naproxen for meloxicam once a day 15 mg or ibuprofen thrice a day 600 mg (NSAID 2). The fourth step included the substitution of the NSAID for tramadol (thrice a day 50 mg).

In this study the proportion of patients responding to paracetamol, NSAID 1 and 2 (NRS ≤ 4) were examined.

## Baseline data and data on previous treatments

Baseline data were collected on demographic and disease-related characteristics using a standardised interview and physical examination. Data on previously used treatment modalities concerning knee and/or hip OA were obtained using a standardised interview consisting of a checklist with all common prescribed analgesics (only analgesics used for at least 14 consecutive days were counted; no exact dosages were required), intra-articular injections, supplements (i.e. glucosamine and chondroitin) and physical therapy (minimum attendance to two sessions was required). In addition, every referred patient was asked to bring a list from the pharmacist or general practitioner with past prescribed medication to the first visit at the outpatient clinic.

## Radiographs

Bilateral (posterior-anterior fixed flexion and lateral) knee and pelvic radiographs were performed in all participants. Scoring of radiographs was done using Kellgren-Lawrence Grading Scale (K&L-score)[19] by an experienced rheumatologist and a research physician (GS).

## Numeric Rating Scale (NRS) and questionnaires

At each visit the NRS pain and NRS patient global assessment (PGA) (0-10) were asked. At baseline, patients were asked to fill out the Knee/Hip injury and Osteoarthritis Outcome Score (KOOS/HOOS) (Likert-scale version) questionnaire.[20;21] These questionnaires include the Western Ontario McMaster Universities (WOMAC)[22] score index in its complete and original format (with permission, http://www.koos.nu). WOMAC pain, stiffness and function subscales were calculated at baseline and after 12 weeks and presented as normalised scores (0 to 100, where 0 equals no symptoms). To assess quality of life, the Short Form-36 (SF-36)[23] questionnaire was completed by all participants. The SF-36 consists of eight subscales with a score range of 0 to 100, where 100 represents the best possible health situation. The physical (PCS) and mental component summary (MCS) scores were calculated as weighted means of the four physical and four mental subscale scores, respectively (higher scores indicate better health situation).

## Outcome

The outcome of this study was the proportion responders (i.e. percentages patients reaching a NRS pain ≤ 4 after each step from the abovementioned treatment protocol), after four weeks use of paracetamol, after four weeks use of NSAID 1 after failing paracetamol and after four weeks use of NSAID 2 after failing paracetamol and NSAID 1. Previous research has shown that the proportion of patients fulfilling NRS pain ≤ 4 was comparable to the proportion OMERACT-OARSI responders[24] after 12 weeks treatment according to the protocol (39 vs. 47 %, respectively).[16] Independent predictors for response to treatment were identified. Furthermore, reasons for non-compliance to the study protocol were collected.

### Statistics

Statistical analyses were performed using STATA/IC 10.1 for Windows. Descriptive statistics were provided by using mean (SD), median (p25-p75) or frequencies/percentages depending on the distribution of data. To calculate the response percentage to NSAID 1 individuals who started the first NSAID (regardless of previous use of paracetamol) were taken together. Moreover, to calculate the response percentage to NSAID 2, individuals who started the second NSAID in the second or third step were analysed together. Around the proportion of responders 95%-confidence intervals (95%-CIs) were calculated. An exploratory sample size calculation was made as follows: to be able to estimate a response proportion with a 95%-CI of ≤ 0.1, an alpha of < 0.05 and a power of 0.8, 80 patients were necessary per group.

To predict a treatment response (NRS pain ≤ 4 after paracetamol or first NSAID), a prediction model was built. Predefined candidate (baseline) predictive variables were: WOMAC subscales, NRS PGA, age, gender, BMI, K&L-score, index joint (knee or hip), number of previously used NSAIDs, previous use of paracetamol, paracetamol continued when NSAID was initiated (paracetamol add-on, solely to predict response to NSAID), duration of knee/hip complaints, and MCS. These variables were first bivariately tested and, if an association with treatment response was found (p of removal > 0.20), entered in a multivariate logistic regression analysis. Using backward selection (based on p-values), the final model was built. For the (possible) predictors odds ratio's (OR's) with 95%-CI were calculated.

In individuals with incomplete data on possible predictors (i.e. WOMAC pain: n = 23, WOMAC stiffness: n= 81, WOMAC physical function: n=28, BMI: n=25, duration of knee/hip complaints: n=30, NRS PGA: n=6, and MCS: n=39), single imputation was performed using regression modelling to replace missing values. Individuals with missing data on response status, i.e. missing values on NRS pain (n=32 after initiation of NSAID 1; n= 12 after initiation of NSAID 2), were classified as non-responder.

### Ethical considerations

The standardised treatment protocol was performed as routine clinical care in the Sint Maartenskliniek. The local Medical Research Ethics Committee (MREC), region Arnhem-Nijmegen (The Netherlands) approved the study design of CONTROL-PRO (local study number 2009/095).

## RESULTS

Between July 2007 and October 2010, 559 patients were treated at the specialised knee/hip OA outpatient clinic. A total of 347 patients fulfilled inclusion and exclusion criteria (Figure 1). Twelve cases had insufficient data due to loss of follow-up (n = 12). Sixty patients were treated not in accordance to the protocol: intra-articular injections (n = 12), tramadol (n = 23), and NSAID combined with paracetamol (n = 25), respectively. In 30 patients no pharmacological therapy was started at study start. Those patients were not included in the statistical analyses. Out of 347 patients 307 (88%) patients were referred

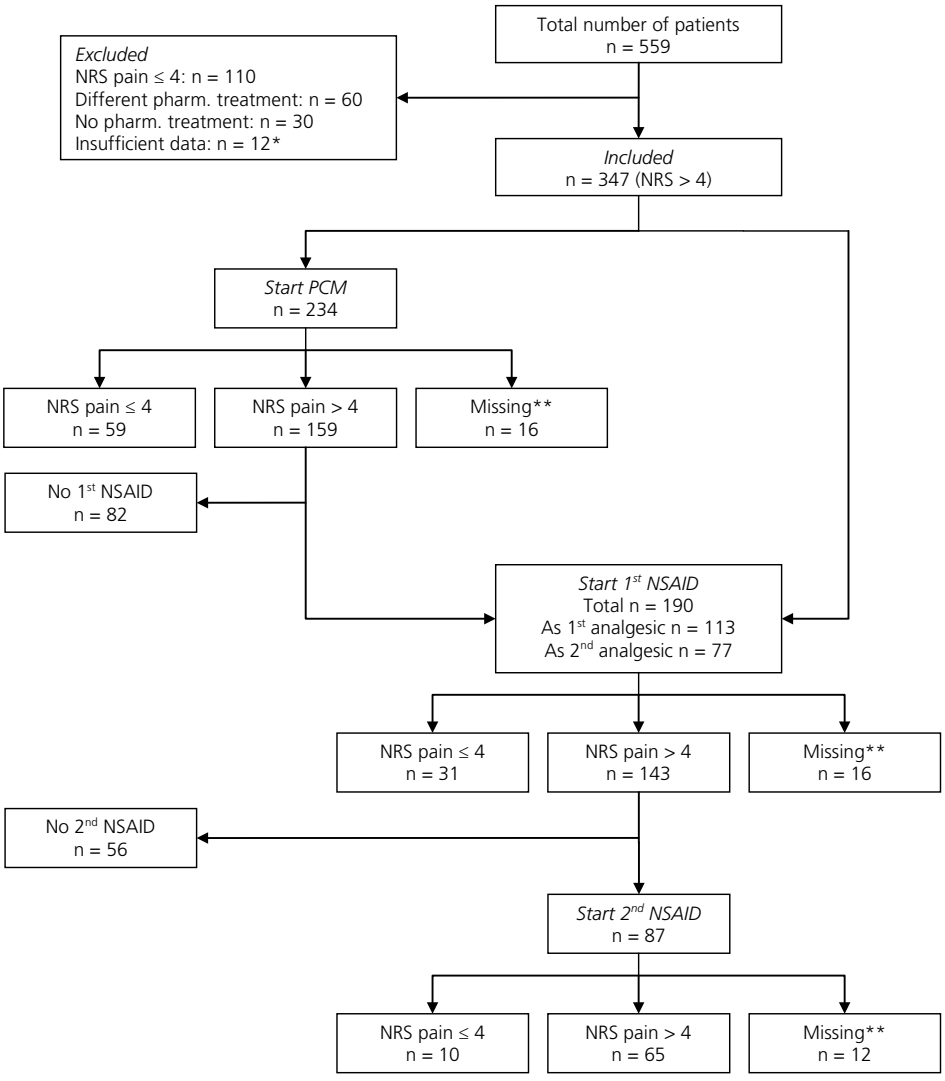


**Figure 1.** Study flowchart.
***** Insufficient data: no available NRS pain at baseline or < 1 follow-up visit ** Missing value on NRS pain; **NRS** numeric rating scale; **NSAID** non-steroidal anti-inflammatory drug; **PCM** paracetamol (acetaminophen)**; pharm.** pharmacological

to the specialised outpatient clinic by an orthopaedic surgeon, whereas the remaining 19 (5%) and 21 (6%) patients were referred by a rheumatologist and a general practitioner, respectively. Baseline characteristics are depicted in Table 1. A total of 234 (67%) patients was treated with paracetamol in the first step. A NSAID was the pharmacological treatment in the first step of 113 (33%) patients (Figure 1).

**Table 1.** Baseline characteristics of patients (n= 347)

| **Variable** | |
|---|---|
| Women, n (%) | 231 (67) |
| Age (years), mean (SD) | 55 (10) |
| BMI, mean (SD) | 29 (5) |
| Knee OA, number (%) | 286 (82) |
| Duration of knee/hip complaints (years), median (p25-75) | 4 (2-10) |
| K&L-score ≥ 2, number (%) | 226 (65) |
| NRS pain (0-10), mean (SD) | 7 (1) |
| NRS patient global assessment (0-10), mean (SD) | 7 (2) |
| WOMAC pain (0-100), mean (SD) | 55 (18) |
| WOMAC stiffness (0-100), mean (SD) | 60 (21) |
| WOMAC function (0-100), mean (SD) | 56 (18) |
| MCS (possible range 2 – 74)* | 50 (11) |
| PCS (possible range 4 – 71)* | 33 (7) |
| Past treatment, number (%) | |
| Analgesics | |
| None | 58 (17) |
| Paracetamol (acetaminophen) | 214 (62) |
| Paracetamol in adequate dose[1] | 71 (20) |
| One or more NSAID | 249 (72) |
| Opioids[2] | 54 (16) |
| Supplements[3] | 130 (37) |
| Physical therapy | 223 (64) |
| Past surgical treatments for knee OA, number (%) | |
| One or more arthroscopies[4] | 165 (58) |
| Open procedures[5] | 39 (14) |
| Past surgical treatments for hip OA, number (%) | |
| One or more arthroscopies | 0 |
| Open procedures | 7 (11) |

* Norm-based scores, higher scores indicate better health, individual scores in the 45-55 range indicate average health; [1]Adequate dose: 2-4 times 1000 mg/day during at least 14 consecutive days; [2]Including tramadol, [3]Glucosamine and chondroitin, [4]Including partial meniscectomy, [5]Including joint prosthesis; **BMI** body mass index; **OA** osteoarthritis; **K&L-score** Kellgren-Lawrence Grading Scale; **NRS** numeric rating scale; **NSAID** non-steroidal anti-inflammatory drug; **MCS** Mental Component Score of Short Form-36; **PCS** Physical Component Score of Short Form-36; **WOMAC** Western Ontario McMaster Universities Osteoarthritis Index

## Outcome

Fifty-nine of the 234 patients (25%, 95%-CI 19-31) reached a NRS pain ≤ 4 after four weeks treatment with paracetamol. A total of 190 individuals was treated with NSAID 1 (i.e. 77 after failing paracetamol in the first step and 113 after insufficient perceived effect from recent use of paracetamol prior to this study), which resulted in a response rate of 31 / 190 (16%, 95%-CI 10-22) patients responding. Eighty-seven patients were treated with NSAID 2 which resulted in 10 / 87 cases (11%, 95%-CI 4-18) in a NRS pain ≤ 4.

The following variables were bivariately associated with a response to paracetamol: higher age, better NRS PGA, lower WOMAC pain, lower WOMAC stiffness, lower WOMAC physical function, higher K&L-score, no past use of paracetamol, and low number of previously used NSAIDs (Table 2). Higher age, lower NRS PGA, lower WOMAC stiffness and higher K&L-score were independently associated with a higher chance of response to paracetamol (Table 4). Lower NRS PGA, lower WOMAC pain, stiffness and physical function were bivariately associated with a higher chance for a treatment response to NSAID 1. Continuing paracetamol when NSAID 1 was initiated was not associated with response to NSAID 1 (Table 3). However, only lower NRS PGA was identified as independent predictor for a response to NSAID 1 (Table 4). The index joint (knee or hip) was not associated with response to paracetamol or NSAIDs.



**Table 2.** Results of univariate logistic regression analysis of possible predictors (at baseline) for treatment response to paracetamol (n= 234)

| Variable | OR | 95% CI |
|---|---|---|
| Gender (male) | 1.10 | 0.61 – 2.01 |
| Age | 1.04 | 1.01 – 1.07 |
| Index joint (knee) | 1.87 | 0.91 – 3.82 |
| NRS PGA | 0.80 | 0.67 – 0.95 |
| WOMAC pain | 0.98 | 0.96 – 1.00 |
| WOMAC stiffness | 0.98 | 0.97 – 1.00 |
| WOMAC physical function | 0.98 | 0.96 – 0.99 |
| BMI | 0.98 | 0.93 – 1.00 |
| Duration of complaints, in years | 0.99 | 0.93 – 1.04 |
| K&L-score | 1.47 | 1.13 – 1.91 |
| Previous use of paracetamol (yes) | 0.51 | 0.28 – 0.94 |
| Number of previously used NSAIDs | 0.74 | 0.56 – 0.97 |
| MCS | 0.99 | 0.96 – 1.01 |

**OR** odds ratio; **CI** confidence interval; **NRS** numeric rating scale; **PGA** patient global assessment; **WOMAC** Western Ontario McMaster Universities score; **BMI** body mass index; **K&L-score** Kellgren-Lawrence Grading Scale; **NSAIDs** non-steroidal anti-inflammatory drugs; **MCS** Mental Component Score of Short Form-36

**Table 3.** Results of univariate logistic regression analysis of possible predictors (at baseline) for treatment response to NSAID 1 (n= 190)

| Variable | OR | 95% CI |
|---|---|---|
| Gender (male) | 0.92 | 0.39 – 2.14 |
| Age | 1.02 | 0.96 – 1.06 |
| Index joint (knee) | 0.90 | 0.32 – 2.55 |
| NRS PGA | 0.71 | 0.56 – 0.89 |
| WOMAC pain | 0.97 | 0.95 – 0.99 |
| WOMAC stiffness | 0.98 | 0.96 – 1.00 |
| WOMAC physical function | 0.97 | 0.95 – 1.00 |
| BMI | 1.04 | 0.97 – 1.11 |
| Duration of complaints, in years | 1.03 | 0.99 – 1.06 |
| K&L-score | 1.39 | 0.98 – 1.97 |
| Previous use of paracetamol (yes) | 1.34 | 0.37 – 4.83 |
| Paracetamol add on* (yes) | 1.45 | 0.61 – 3.43 |
| Number of previously used NSAIDs | 0.75 | 0.57 – 1.00 |
| MCS | 1.03 | 0.99 – 1.07 |

* In the first 44 patients with no response to paracetamol as first step of the protocol, paracetamol was continued when first NSAID 1 was started at the second step
**OR** odds ratio; **CI** confidence interval; **NRS** numeric rating scale; **PGA** patient global assessment; **WOMAC** Western Ontario McMaster Universities score; **BMI** body mass index; **K&L-score** Kellgren-Lawrence Grading Scale; **NSAIDs** non-steroidal anti-inflammatory drugs; **MCS** Mental Component Score of Short Form-36

### Non-adherence to protocol

A total of 138 out of 302 (46%) patients did not start with a (new) NSAID after failing paracetamol or the first NSAID (i.e. persistent NRS > 4) (Figure 1). Reasons for these protocol-violations were: pain-level acceptable 17 / 138 (12%) and unwillingness to take a NSAID 53 / 138 (39%). In 39 out of 138 cases (28%) no reason for the protocol-violation could be identified, possibly reflecting inadequately offering the next step of the protocol by the caregiver. Other reasons for no switch to a (new) NSAID were: contra-indication (10 / 138, 7%) and start of different pharmacological treatment (19 / 138, 14%).

## DISCUSSION

This is the first study analysing a NRS-guided pain management strategy in daily knee and hip OA care. Our study shows that NRS-tailored use of paracetamol results in a response percentage of 25% and that treatment with a NSAID after failing paracetamol leads to a treatment response of 16% in secondary care knee and hip OA patients. Treatment with

**Table 4.** Prediction models with independently predictors for response to paracetamol (n= 234) and first NSAID (n = 190)

| Variable | OR | 95% CI |
|---|---|---|
| *Response to paracetamol* | | |
| Age | 1.03 | 1.00 – 1.07 |
| NRS PGA | 0.80 | 0.66 – 0.97 |
| WOMAC stiffness | 0.98 | 0.96 – 0.99 |
| K&L-score | 1.43 | 1.07 – 1.92 |
| $R^2$ = 0.11; AUC 0.74 | | |
| *Response to first NSAID* | | |
| NRS PGA | 0.71 | 0.56 – 0.89 |
| $R^2$ = 0.05; AUC 0.66 | | |

**OR** odds ratio; **CI** confidence interval; **NRS** numeric rating scale; **PGA** patient global assessment; **WOMAC** Western Ontario McMaster Universities score; **K&L-score** Kellgren-Lawrence Grading Scale; **AUC** area under the curve **NSAIDs** non-steroidal anti-inflammatory drugs



a second NSAID after failing paracetamol and the first NSAID resulted only occasionally in a treatment response (i.e. 11%). We therefore conclude that prescription of paracetamol and prescription of a NSAID after insufficient results with paracetamol are of value in knee and/or hip OA patients referred to secondary care, even after considering joint replacement. Some predictors for response to paracetamol and a NSAID were identified - including patient- and disease related factors - however, no strong predictors were found.

The percentage protocol violations, i.e. no switch of analgesic or switch to an agent not according to the protocol, was 46%. This proportion is comparable with data from a post-hoc analysis in a RCT in rheumatoid arthritis in which rheumatologists were advised about the right methotrexate dose according to the protocol before each visit, but were allowed to deviate from the protocol.[25] In 51% of these protocol violations no medication switch - although appropriate according to the protocol - was performed because patients perceived their pain level as acceptable and/or were unwilling to try a (new) NSAID. Possibly, these results reflect fear for adverse events of NSAIDs and the individual variation in the patient acceptable symptom state (PASS). The mean PASS for pain lies below 4 (32 mm (95%-CI 30-35) for knee OA and 35 mm (95%-CI 33-37) for hip OA on a 100 mm visual analogue scale), but our study indicates that a considerable proportion of patients reports a PASS beyond 4.[26]

The internal validity of our study seems adequate, illustrated by ample precision. However, the uncontrolled design should urge to caution regarding conclusions to be drawn about the effect of the interventions. Improvement of symptoms could also, at least partly, be explained by regression to the mean (natural history) or expectation bias (placebo effect). However, spontaneous regression of complaints seems to be an unlikely explanation because the waiting time for our outpatient clinic was approximately two to

three months before inclusion. Also, the response percentages found in this study seem comparable to the differences between the intervention and placebo arm in analgesic trials,[27] and improvement was rarely seen after the second NSAID. Therefore, we conclude that the occurrence of type I errors is unlikely.

The response percentages with paracetamol could be inflated by effects of the other treatment modalities offered during the baseline visit. However, the effects of physical therapy are not to be expected within the first 4 weeks as there was usually a waiting list of a few weeks before attendance.

Adherence to prescribed medication is known to be a potent effect modifier in clinical practice. Since adherence to prescribed treatment was not routinely measured in this study, non-adherence to prescribed treatment modalities could have resulted in lower response percentages. Nevertheless, this pragmatic study was intended to estimate and compare the results of paracetamol and NSAIDs in addition to non-pharmacological interventions in daily clinical practice, thus including the effects of non-adherence.

Generalizability of the results of our study seems limited to symptomatic knee and hip OA patients in secondary care. In this light, our cohort is comparable with other cohorts, consisting mainly of obese women with knee OA.[28;29] Level of pain and BMI, however, are higher and patients were younger, possibly reflecting some selection as the vast majority of patients was referred by orthopaedic surgeons mostly because of absence of an indication for joint replacement surgery. Also, relatively high rates of surgical procedures in the past (in the knee OA group) exist in current study.

Predicting a treatment response to pharmacological interventions with pre-treatment variables could be valuable as it could result in prevention of unnecessary exposure to potentially toxic agents. However, we were unable to identify strong independent predictors for response to paracetamol or NSAIDs. Higher K&L-scores as predictor for response to paracetamol has never reported before, though it is an additional argument to try paracetamol before considering joint replacement even in advanced knee and hip OA. In a recently published study on predictors of response to cyclo-oxygenase-2 (COX-2) inhibitors, the only consistent predictor for an OMERACT-OARSI response was WOMAC physical function.[30] Other studies report various, but no consistent predictors for treatment response to NSAIDs.[31;32] Possibly, the response to pharmacological agents is determined by other non-measured variables.

Future research should be focussed on improvement of the pharmacological treatment strategy of symptomatic knee and hip OA, e.g. the place of (partial) opioids, paracetamol combined with a NSAID and intra-articular injections combined with analgesics. Furthermore, the ideal treatment strategy could possibly be improved with shortening the trial period of a pharmacological agent, as the response after two weeks treatment with COX-2 inhibitors in two randomised controlled trials was a strong predictor of OMERACT-OARSI response at 12-weeks treatment.[33] Another study showed similar results for paracetamol.[34] Also, n of 1 trials could be used to discover the best treatment for an individual person, in which patients are exposed to different analgesics during short trial periods.[35] Finally, development of novel classes symptom reducing agents should be encouraged, although precaution of side effects is warranted.[36]

In conclusion, protocolised prescription of paracetamol and a NSAID after failing paracetamol resulted in moderate treatment response percentages, whereas the results of switching between NSAIDs were disappointing in secondary care knee and hip OA patients in daily clinical practice. Response to paracetamol or a NSAID could largely not be predicted. We therefore conclude that prescription of paracetamol, and prescription of a NSAID after insufficient results with paracetamol, is appropriate in patients with severe knee or hip OA, even after prior consideration for joint replacement. Reasons for non-compliance to initiation of analgesics should be further investigated.

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# 6

# FATIGUE IN KNEE AND HIP OSTEOARTHRITIS: THE ROLE OF PAIN AND PHYSICAL FUNCTION

# ABSTRACT

**Objectives** It is suggested that serious levels of fatigue are present in nearly half of patients with osteoarthritis (OA). However, it is unclear which dimensions of fatigue are involved, if fatigue is related to pain and daily functioning, and if fatigue is influenced by therapy. The aims of this study were to measure levels of different dimensions of fatigue before and after evidence-based conservative treatment and to investigate the association between fatigue and pain and physical function in patients with knee or hip OA.

**Methods** In this observational cohort study, levels of different dimensions of fatigue were measured in knee and/or hip OA patients before and after 12 weeks of conservative treatment. The cross-sectional and longitudinal relation between (change in) fatigue dimensions and (change in) pain or physical function were studied using association models, controlling for predefined possible confounders.

**Results** A total of 231 patients was included, with 47% experiencing severe fatigue. A small decrease in levels of fatigue was seen after standardised treatment. The level of fatigue severity was cross-sectionally and longitudinally associated with physical function, whereas the level of physical fatigue was cross-sectionally and longitudinally associated with pain and physical function. No confounders were identified.

**Conclusion** Important levels of fatigue are common in knee and hip OA patients. After evidence-based tailored conservative treatment targeted to improve pain and physical function a small decrease of fatigue levels has been found. Reduction of levels of different fatigue dimensions were related to change in physical function and pain.



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# INTRODUCTION

In patients with chronic diseases, fatigue is often rated as one of the key factors leading to a decreased quality of life.[1] Regarding osteoarthritis (OA), a focus group study indicated that OA patients experience notable amounts of fatigue that has substantial impact on their lives.[2] The few studies on fatigue in OA report marked levels of fatigue in nearly half of patients.[3-6] These findings are comparable with levels found in rheumatoid arthritis (RA).[4]

Cross-sectional and some longitudinal data show that a large amount of variability exists in (the course of) fatigue in OA patients.[4;5] Therefore, identifying variables associated with (change in) fatigue could be valuable. Gaining more insight into these factors leads to more insight into the pathophysiology of fatigue in OA. Moreover, modifying these factors may lead to reduction of fatigue experienced by OA patients. Up to now, several factors associated with fatigue in OA have been identified, such as: older age, more pain, less physical activity, lower positive affect, depression and lower c-reactive protein (CRP) in serum.[4;5;7] Of these factors, especially the influence of mental health (depression in particular) and other psychosocial factors on fatigue seems to be substantial.[5;6] What is more, depression may be a factor on the causal pathway between physical function and fatigue.[8]

Studies concerning fatigue in OA published thus far have some limitations. First, included subjects were inadequately characterised, without use of widely accepted classification criteria.[9;10] Second, no distinction between different dimensions of fatigue – like for example, subjective fatigue, concentration, motivation and physical activity - was made. It could be hypothesized that increased levels of fatigue solely exist in particular dimensions and that each dimension has different determinants. Lastly, aforementioned studies were mostly cross-sectional and non-interventional, thus limiting the possibility to draw conclusions about direction of causality.

Fatigue severity in OA seems to be related with clinical and psychological factors; however, the precise causal pathway remains unclear. It could be conceived that increased fatigue in OA is mainly caused by increased pain and/or decreased physical function. This is indeed supported by studies targeting fatigue in RA.[11;12] Improvement in pain and physical functioning as recommended in treatment guidelines for knee and hip OA[13-17] should – following this line of reasoning – lead to lower levels of fatigue, but this has not been studied yet.

The aims of this study were therefore 1) to investigate levels of different dimensions of fatigue in knee and hip OA and 2) to assess changes in fatigue after evidence-based tailored conservative treatment targeting to reduce pain and physical functioning and 3) to study the cross-sectional and longitudinal relations between (change in) fatigue with (change in) pain and physical function in patients with knee and/or hip OA.

# PATIENTS AND METHODS

## Design

Levels of different dimensions of fatigue were measured in an observational cohort study before and after evidence-based tailored multimodal conservative treatment in knee

and hip OA patients. Subsequently, the cross-sectional and longitudinal relation (after 12 weeks of standardised treatment) between the fatigue dimensions and the supposed determinants pain and physical function were studied.

## Patients

All patients referred to the specialised knee/hip OA outpatient clinic ('knie/heup artrose poli') at the department of Rheumatology of the Sint Maartenskliniek and participating in the COhort of Non-invasively TReated Osteoarthritis of Lower extremities - Pain, function and Radiological Outcome (CONTROL-PRO) study were considered for inclusion in this study. The main objective of the CONTROL-PRO study is to investigate the disease course of patients with moderately advanced (secondary care) knee and hip OA, receiving standardised non-invasive multimodal treatment.

For participation in CONTROL-PRO, patients had to fulfil the clinical American College of Rheumatology (ACR) criteria for knee and/or hip OA.[9;10] For knee OA the following criteria were used: knee pain (> 15 days of last month) plus at least three of the following: age > 50 years, morning stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth. For hip OA the following criteria were used: hip pain (> 15 days of last month) plus internal rotation of the hip < 15° and erythrocyte sedimentation rate (ESR) ≤ 45 mm/hr or hip pain (> 15 days of last month) plus internal rotation of the hip ≥ 15° and painful internal rotation of the hip and morning stiffness ≤ 60 minutes and age > 50 years.

Exclusion criteria were: inflammatory rheumatic diseases or deposition diseases possibly leading to inflammatory arthritis or secondary OA, co-morbidity exceeding the complaints of limitations of knee or hip OA, cognitive or sensomotor problems interfering with the use of questionnaires and planned orthopaedic procedures within the next 12 weeks. Allowed were calcium pyrophosphate deposition disease (CPPD) (excluding the phenotypes pseudogout and polyarthritis) and previous meniscus problems.

## Standardised conservative treatment

Patients who were treated at the knee/hip OA outpatient clinic received standardised evidence-based tailored conservative treatment in a stepped-care format as usual care for 12 weeks if they experienced knee and/or hip pain on a numeric rating scale (NRS, 0 - 10) higher than 4. The stepped-care model was based on a Dutch multidisciplinary guideline (published online) for diagnosis and treatment of knee and hip OA and has been proposed by a consensus panel of leading experts in the field of OA in The Netherlands.[18;19]

The goal of the intervention was to reduce the level of pain on the NRS to 4 or lower. The study visits were planned at week 0 and 12 at the outpatient clinic and at week 4 and 8 by telephone and managed by a research physician (GS), a physician assistant or a nurse practitioner (MA). When NRS pain remained higher than 4 and patients had adequately taken the prescribed medication for at least two weeks, treatment options outlined in the next step of the stepped-care model were offered.

The first step of the treatment protocol consisted of education, life style advice concerning physical activity and weight loss in patients with a body mass index (BMI) of 28

or higher (goal 5% weight loss in 12 weeks), referral for physical therapy (prescription for both aerobic and strengthening exercises according to the graded activity principle[20]), and treatment with paracetamol (acetaminophen) in a fixed dose of thrice a day 1000 mg (in case of no recent use for knee and/or hip complaints). In the second step, if necessary, and no earlier than after 4 weeks a Non-Steroidal Anti-Inflammatory Drug (NSAID) was added. Our preferential order being naproxen twice a day 500 mg, followed by substitution for meloxicam once a day 15 mg, or ibuprofen thrice a day 600 mg at week 8 when necessary (step 3). Step 4 includes the substitution of the NSAID for tramadol (thrice a day 50 mg).

To patients with a NRS pain ≤ 4 at baseline all modalities of the protocol were offered, but no new analgesics were prescribed.

## Measurement instruments

### *Fatigue*

Fatigue was assessed by the Checklist Individual Strength (CIS).[21] This 20-item patient assessed questionnaire consists of 4 subscales: 1) fatigue severity (CIS-fatigue, 8 items, range: 8-56, for example "I feel tired"), 2) reduction in concentration (CIS-concentration, 5 items, range: 5-35, for example "My thoughts easily wander"), 3) reduction in motivation (CIS-motivation, 4 items, range: 4-28, for example "I feel no desire to do anything") and 4) reduction in physical activity (CIS-activity, 3 items, range: 3-21, for example "I don't do much during the day"). Each item is scored on a 7-point Likert scale. Furthermore, CIS-fatigue was divided into three classes: 1) 'normal' experience of fatigue (normal fatigue) when scores below 27 were measured (mean score for healthy controls plus one standard deviation (SD)[22]), 2) 'moderate' experience of fatigue (moderate fatigue) when scores lie between 27 and 34 and 3) 'severe' experience of fatigue (severe fatigue) when values of 35 or higher were calculated (scores comparable with fatigue as experienced by patients with chronic fatigue syndrome).[21] The CIS has proven to be a reliable and valid instrument in various conditions.[22-24]

### *Pain, patient global assessment, stiffness and physical functioning*

To measure pain, stiffness and physical functioning the Likert scale version of the Knee/Hip injury and Osteoarthritis Outcome Score (KOOS / HOOS) questionnaire was used. KOOS / HOOS questionnaires include the Western Ontario McMaster Universities OA index (WOMAC) in its complete and original format (with permission, http://www.koos.nu). WOMAC pain, stiffness and function subscales were calculated (0 to 100, where 0 equals no symptoms). In addition, patient global assessment (PGA) of OA severity was measured using a NRS (0 - 10).

## Radiographs

Bilateral (posterior-anterior, fixed flexion and lateral) knee and pelvic radiographs were performed in all participants.[25] The joint with most complaints at baseline was graded according to the Kellgren-Lawrence grading scale (K&L-score).[26] All radiographs were read by an experienced rheumatologist and/or a trained research physician (GS).

### Data collection and management

Demographics, radiographs and data on previously used treatment modalities concerning knee and/or hip OA and data on symptoms were obtained in all patients. Questionnaires were collected at baseline and after 12 weeks.

### Statistics

Statistical analyses were performed using STATA/IC 10.1 for Windows. In patients with incomplete baseline or follow-up data, multiple imputation was performed using regression modelling to replace missing values. Descriptive statistics were provided. Levels of fatigue before and after 12 weeks treatment were compared using a $\chi^2$-test (for nominal variables), a paired t-test or Wilcoxon signed-rank test (for continuous variables, depending on distribution). The subscale CIS-fatigue was divided into three classes as mentioned above. Effect sizes (ES) were, when applicable, calculated using the following formula: difference between mean before and mean after the intervention divided by the SD of the variable.

Although pain and physical function were relative highly correlated (r = 0.83), the variance inflation factor (VIF) indicated no problematic multicollinearity (VIF = 3.2).

Association models were built with one of the fatigue dimensions as dependent variable and both pain (WOMAC pain) and physical function (WOMAC function) as central determinants. Regarded as potential confounders were: age, gender, body mass index (BMI), index joint (knee or hip), duration of complaints, K&L-score, and past treatment. The variables were added to the model one by one to test for possible confounding (cut-off for relevant change in the regression coefficient (β) of physical functioning and pain was 10% or more). The same procedure was followed to study the association of change in fatigue after 12 weeks (dependent variable) with change in pain and physical functioning as central determinants. All models were checked for heteroscedasticity and non-normality of residuals using visual inspection of residual plots.

### Ethics

The local Medical Research Ethics Committee (MREC), region Arnhem-Nijmegen (The Netherlands) approved the study design of CONTROL-PRO (local study number 2009/095). Moreover, all procedures followed were in accordance with the Helsinki Declaration. All participants gave their written informed consent.

## RESULTS

Between April 2008 and February 2010, 292 knee and/or hip OA patients fulfilled inclusion criteria of which 231 had sufficient follow-up data (Table 1). Main reason for insufficient data was loss of follow-up. No clinical relevant baseline differences were found between patients with and without sufficient follow-up data.

Data regarding CIS subscales are depicted in Table 2. Patients with knee and/or hip OA in our study experienced significantly more fatigue in two dimensions (CIS-fatigue and

**Table 1.** Baseline characteristics of patients (n=231)

| Variable | |
|---|---|
| Women, n (%) | 150 (65) |
| Age (years), mean (SD) | 54 (10) |
| BMI, median (p25-75) | 28 (25-32) |
| Knee OA, n (%) | 192 (83) |
| Duration of knee or hip complaints (years), median (p25-75) | 4 (2-11) |
| K&L-score ≥ 2, n (%) | 128 (56) |
| Past treatment, n (%) | |
| Analgesics | |
| Paracetamol in adequate dose[1] | 62 (27) |
| One or more NSAID's | 158 (68) |
| Physical therapy | 148 (64) |
| NRS pain (0-10), mean (SD) | 5.9 (2.1) |
| NRS PGA (0-10), mean (SD) | 6.3 (2.2) |
| WOMAC pain (0-100), mean (SD) | 53 (22) |
| WOMAC stiffness (0-100), mean (SD) | 57 (24) |
| WOMAC function (0-100), mean (SD) | 54 (23) |

Higher scores indicate poorer outcome unless stated otherwise.
[1]Adequate dose: 2-4 times 1000mg/day during at least 14 consecutive days; [2] Higher score indicates better outcome. **BMI** body mass index; **OA** osteoarthritis; **K&L-score** Kellgren-Lawrence Grading Scale; **paracetamol** acetaminophen; **NSAID** non-steroidal anti-inflammatory drug; **NRS** numeric rating scale; **PGA** patient global assessment; **WOMAC** Western Ontario McMaster Universities score.

**Table 2.** Levels of fatigue dimensions before and after standardised conservative treatment (n=231)

| Variable | Baseline | Week 12 | Change | 95 % CI | ES |
|---|---|---|---|---|---|
| *CIS-fatigue* | 31.8 (13.6) | 30.2 (13.6) | - 1.6 | - 0.3 to - 3.0 | 0.12 |
| CIS-concentration | 13.8 (8.1) | 13.1 (7.8) | - 0.8 | -1.6 to 0.07 | - |
| CIS-motivation | 11.9 (6.2) | 11.3 (5.6) | - 0.6 | - 1.3 to 0.06 | - |
| *CIS-activity* | 12.1 (5.5) | 11.1 (5.6) | - 1.0 | - 0.4 to - 1.6 | 0.18 |
| Severe fatigue (%)[1] | 47.2 | 36.8 | - 10.4 | | |
| Moderate fatigue (%)[1] | 19.1 | 22.9 | 4.0 | | |
| Normal fatigue (%)[1] | 33.8 | 40.3 | 6.5 | | |

Numbers are mean (SD) unless stated otherwise. [1] CIS-fatigue was divided into 3 classes: Normal fatigue (CIS-fatigue < 27), Moderate fatigue (CIS-fatigue between 27 and 35), Severe fatigue (CIS-fatigue 35 or higher). **CIS** Checklist Individual Strength; **ES** effect size

CIS-activity) compared to data on healthy controls from the literature (31.8 versus 17.3 and 12.1 versus 6.6, respectively).[24;27] A total of 28/231 (12%) participants received only non-pharmacological treatment during the 12-week treatment period, whereas all other individuals had at least one additional pharmacological intervention.

At the group level, there was a small (significant) decrease of CIS-fatigue and CIS-activity after 12 weeks evidence-based tailored conservative treatment. At baseline, 109 patients (47%) met the criteria for severe fatigue (i.e. CIS-fatigue ≥ 35) and this decreased to 85 patients (37%) after 12 weeks.

After 12 weeks of evidence-based tailored conservative treatment improvements in NRS pain (from 5.9 to 4.9, $p < 0.001$, ES = 0.48), WOMAC pain (from 53 to 47, $p < 0.001$, ES = 0.27) and physical function (from 54 to 47, $p < 0.001$, ES = 0.31) were found.

In the cross-sectional model (Table 3), physical function was independently associated with CIS-fatigue at baseline. Pain was not independently associated with CIS-fatigue. Physical function was also independently associated with CIS-activity at baseline. For the cross-sectional model no confounders were identified.

In the longitudinal model (Table 4), change in CIS-fatigue after 12 weeks conservative treatment was not associated with baseline physical function and pain levels. However, change in CIS-fatigue was independently associated with improvement of physical function. No confounders could be identified for this relation. Change in CIS-fatigue was not associated with improvement of pain. Change in CIS-activity after 12 weeks conservative treatment was not associated with baseline physical function and pain levels. However, change in CIS-activity was independently associated with improvement of pain and physical function. No confounders could be identified for this relation.

**Table 3.** Cross-sectional association model with baseline fatigue scores as dependent variables and WOMAC-subscales as central determinants

| **Variable** | β | **95 % CI** |
|---|---|---|
| *CIS-fatigue* | | |
| WOMAC function | 0.38 | 0.27 to 0.50 |
| WOMAC pain | - 0.08 | - 0.20 to 0.04 |
| $R^2 = 0.29$ | | |
| *CIS-activity* | | |
| WOMAC function | 0.14 | 0.08 to 0.19 |
| WOMAC pain | - 0.06 | - 0.11 to 0.01 |
| $R^2 = 0.16$ | | |

**CIS** Checklist Individual Strength; **WOMAC** Western Ontario McMaster Universities score

**Table 4.** Longitudinal association model with fatigue change scores as dependent variables and changes of WOMAC-subscales as central determinants

| Variable | β | 95 % CI |
|---|---|---|
| *Change in CIS-fatigue* | | |
| Change WOMAC function | 0.12 | 0.01 to 0.23 |
| Change WOMAC pain | - 0.04 | - 0.14 to 0.06 |
| $R^2 = 0.02$ | | |
| *Change in CIS-activity* | | |
| Change WOMAC function | 0.06 | 0.008 to 0.10 |
| Change WOMAC pain | 0.04 | 0.0003 to 0.09 |
| $R^2 = 0.09$ | | |

**CIS** Checklist Individual Strength; **WOMAC** Western Ontario McMaster Universities score

# DISCUSSION

The results of the current study show that levels of fatigue severity, and to a lesser extent physical fatigue, are high in patients with well characterized knee and hip OA, with nearly half of the patients experiencing severe fatigue. Evidence-based tailored conservative treatment resulted in a small decrease of experienced fatigue. Reduction of fatigue severity was found to be related to physical function, whereas reduction of physical fatigue seemed to be related to level of physical function and pain. To our knowledge, this is the first study to evaluate the impact of recommended medical treatment on different dimensions of fatigue in symptomatic OA.

Our study confirms that fatigue, and even severe fatigue, is highly prevalent amongst patients with knee and/or hip OA. This is not only true for fatigue severity, but also for physical fatigue. Motivational fatigue and concentration, however, are not affected. Of note, direct comparison of CIS subscale levels in present study and levels in healthy controls is difficult since the latter consisted of 53 healthy individuals (mean age 31.1, SD 11.5) matched with patients with chronic fatigue syndrome and multiple sclerosis.[24] However, also by indirect comparison it can be assumed that OA patients experience more fatigue (measured with the CIS) than healthy persons as levels of CIS-fatigue in our OA cohort are quite similar with levels in RA patients and RA patients are known to have increased fatigue levels.

The findings in our study are in line with the sparse existing data on fatigue in OA[2;4;5] and underscore that fatigue is indeed an important issue in patients with OA. Measured levels of fatigue are comparable to levels seen in inflammatory rheumatic diseases like RA[3-5;11;12;28] and ankylosing spondylitis[29] and somewhat higher than observed in psoriatic arthritis.[30]

It should be noted that no control group was used, therefore bias by, for example, regression to the mean or placebo effect cannot be ruled out. To our knowledge only one other longitudinal study that assessed fatigue after standardised treatment in OA

is published. This randomised controlled trial assessed the effect of a self-management program in knee OA patients, and found no significant decrease in fatigue and physical function after 12 months, whereas pain decreased significantly.[31] This is in line with the results from present study indicating that fatigue severity is related to improvement of physical function and not to pain.

Regarding the underlying mechanism of fatigue in OA, our data suggest that fatigue severity is partly determined by physical function, whereas physical fatigue is determined by both physical function and pain. These associations where found in both our cross-sectional as well as in our longitudinal analyses. As our standardised treatment included interventions explicitly targeting pain and physical function including life style advice, physical therapy and analgesics, we may conclude that the direction of causality is that decrease of physical function induces more severe fatigue and that decrease in pain, in addition to increase in physical function, improves physical fatigue. The finding that different dimensions of fatigue in rheumatic diseases have different determinants has not been demonstrated yet. A recently published prospective cohort study indicated that fatigue is determined by physical function[8] which is in concordance with our study.

In this study no confounders were identified. However, fatigue certainly depends on other not-measured variables (e.g. psychosocial factors), as indicated by the low to moderate explained variance found. Furthermore, present study was primarily set up to investigate the relation between fatigue and physical function and between fatigue and pain, because these are the main domains targeted in conservative treatment of OA.

The study cohort that was used - symptomatic knee and hip OA in secondary care - is comparable with other cohorts, consisting mainly of obese women with knee OA.[32;33] However, the level of pain and BMI were higher and patients were younger, possibly reflecting some selection to a cohort with individuals with relatively high levels of complaints. This should, however, not have lead to biased inferences.

Future research should be directed to answer several important remaining questions. Although the decreases of levels of fatigue after evidence-based tailored conservative treatment are only modest, it is possible that the maximum effect of the intervention is not yet reached after 12 weeks. Another explanation for that only a moderate effect on fatigue was found could be that individuals with high levels of experienced fatigue are probably unwilling to attend physical therapy or change their life style. Besides, it could be presumed that a more intensive multidisciplinary approach to improve function and pain will result in a more substantial decrease of fatigue levels. Furthermore, given the relatively low ES found, an approach especially targeted to reduce fatigue will have much greater effects. To realize this, more insight is required in the underlying mechanisms regarding fatigue in OA, with for example depression and sleep disturbances[34] being potential causal factors. Targeting these domains could potentially reduce fatigue levels in OA.

In summary, high levels of fatigue are very common in knee and hip OA and are associated with physical function and pain. Evidence-based tailored conservative treatment targeted at improvement of physical function and pain also leads to a small reduction of fatigue levels, with change in fatigue severity being related to physical function and change in physical fatigue being related to pain and physical function.

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# 7

# SUMMARY AND CONCLUSIONS

## GENERAL INTRODUCTION

Osteoarthritis (OA) is the most common rheumatic disease, with the knee and the hip being one of the most affected joints. OA results from an imbalance between synthesis and degradation of the extra-cellular matrix of articular cartilage. Because no disease modifying agents are available up to now, evidence-based treatment options for daily clinical practice are aimed to reduce symptoms and consist of non-surgical and surgical modalities. Non-surgical modalities are divided in non-pharmacological (e.g. education, exercise, weight reduction) and pharmacological (i.e. analgesics) treatment options. The most important surgical treatment option for knee and hip OA is joint replacement. Due to the drawbacks of joint replacement surgery and the increasing incidence of OA in the ageing population, effective conservative treatment for knee and hip OA is highly needed. Therefore, the aim of this thesis was to improve (the use of) conservative treatment for knee and hip OA.

## CHAPTER 2

To assess the OA-related health care utilization, baseline and two-year follow-up data from the nationwide study, Cohort Hip and Cohort Knee ('Cohort Heup En Cohort Knie', CHECK), was analysed. CHECK is a 10-year prospective cohort study of 1002 individuals with early symptomatic OA of hip and/or knee in The Netherlands. Identifying (modifiable) factors that predispose individuals with OA as persistent non-users or high users of health care could help health professionals to optimize the patients' use of health care system. Therefore, the aim of the study presented in Chapter 2 was to describe and predict health care utilization (HCU) over time in individuals with early hip and knee OA.

Six forms of health care services were distinguished: use of analgesics and/or supplements, contact with a general practitioner, an allied health professional, secondary care or alternative care. By use of median split, high-overall users of health care were identified. Participants without HCU at baseline and two years were labelled as persistent non-users.

The results show that the majority of patients reported HCU at baseline and at two years, with no difference between individuals in the hip (n=588) and knee (n=832) group. After two years of follow-up, contact with health care providers decreased in both groups, whereas use of analgesics remained stable. Compromised physical health and previous use of health care were the strongest predictors for future high overall HCU in both groups. Less joint stiffness, better physical health and greater range of motion were the strongest predictors for persistent non-use of the health care system.

## CHAPTER 3

Up to now, no disease modifying OA drug (DMOAD) is available in clinical practice. In recent years, research on possible DMOADs, including doxycycline, is intensified. Doxycycline has been studied before in human OA in one clinical trial, in which doxycycline was found - albeit not the primary study objective - to retard progression of radiographic knee OA,

with a relatively mild toxicity profile. No effect on pain was found, possibly due to low pain scores at enrolment, although flares of pain seemed to occur less frequently. Therefore, the clinical important question whether doxycycline can reduce symptoms of OA was unanswered. Thus, in Chapter 3, the effects on reducing symptoms of doxycycline in knee OA were investigated in a randomised triple-blinded controlled trial. A total of 232 symptomatic knee OA patients were treated with doxycycline or placebo twice a day for 24 weeks to study the effects of doxycycline on OA-related symptoms. At the end of the study, no difference on proportion of patients with a treatment response was found, although a total of 72/232 (31%) met the OMERACT-OARSI responder criteria. Also, no difference in secondary endpoints (i.e. pain, stiffness, physical function, patient global assessment and quality of life) was found. However, individuals treated with doxycycline experienced significantly more adverse events (i.e. sun sensitivity) and more often ceased treatment because of side effects compared to the placebo-group. Therefore, the conclusion was drawn that doxycycline does not exhibit a symptom-modifying effect in knee OA but is associated with an increased chance of toxicity.

## CHAPTER 4

Although interventions recommended in several treatment guidelines have proven to be effective in reducing symptoms of knee and hip OA, the combined efficacy was never investigated. In Chapter 4, the results of implementation of an evidence-based treatment protocol (based on existing treatment guidelines) for symptomatic knee and/or hip OA are presented. This protocol, based on the multidisciplinary patient-centred stepped-care strategy for conservative treatment of hip or knee OA, known as BART ('Behandelstrategie ARTrose', Beating OA), was implemented at a specialised outpatient clinic at the outpatient clinic of the Rheumatology department of the Sint Maartenskliniek. The 183 included patients received standardised evidence-based tailored conservative treatment in a stepped-care format for 12 weeks. The goal of the intervention was to reduce the level of pain on a numeric rating scale (NRS, 0-10) to 4 or lower. The protocol consisted of treatment with analgesics, education, life style advices concerning physical activity, weight loss advices in obese patients and referral for physical therapy. When NRS pain remained higher than 4, a new analgesic was offered. After 12 weeks conservative treatment according to the protocol, 86/183 (47%) patients had reached a treatment response according to the OMERACT-OARSI responder criteria, whereas 71/183 (39%) reached a NRS pain $\leq$ 4. Moreover, improvements of pain, physical function and patient global assessment were found.

A remarkable finding was that the vast majority of patients has not been exposed adequately to conservative treatment modalities for knee and/or hip OA in the past (81%). Particularly physical therapy and paracetamol were under-used. This is striking, especially when keeping in mind that the majority of patients were already considered for joint replacement in secondary care.

The only identified independent predictor for an OMERACT-OARSI response after 12 weeks conservative treatment was the number of previously used non-steroidal

anti-inflammatory drugs (NSAIDs). Therefore, treatment response could largely not be predicted. Possibly other non-measured variables play a role as well.

Consequently, all individuals with symptomatic knee and/or hip OA referred to secondary care have the same chance to respond to conservative treatment and this should be offered before considering joint replacement.

## CHAPTER 5

Studies on pharmacological pain management strategies in OA are lacking. Therefore, an in-dept study of analgesic treatment using an evidence-based treatment protocol was undertaken and described in Chapter 5. The protocol consisted of education, life style advices concerning physical activity and weight loss advices in addition to NRS-guided prescription of analgesics. The first step of pharmacological pain management was treatment with paracetamol in a fixed dose of thrice a day 1000 mg in case of no recent use in adequate dosage. In the second step, if necessary and not earlier than after 4 weeks, a NSAID (NSAID 1) was advised. The next step consisted of substitution of NSAID 1 for NSAID 2. The main outcomes were the proportions of patients reaching a NRS pain ≤ 4 after each step. In addition, predictors for a response (i.e. NRS pain ≤ 4) to paracetamol and NSAID 1 were identified.

A total of 347 patients was included. Of these patients, 234 were treated with paracetamol, 190 with NSAID 1 and 87 with NSAID 2, with response percentages of 25, 17 and 11%, respectively. A few independent predictors for response to analgesics were identified: i.e. higher age, lower patient global assessment, lower stiffness and higher Kellgren & Lawrence grading scale (K&L-score) for response to paracetamol and lower patient global assessment for response to NSAID 1.

A total of 138 out of 302 (46%) patients did not start with a (new) NSAID after failing paracetamol or the first NSAID (i.e. persistent NRS pain > 4). Reasons for failure to follow the advice of the treating physician were mainly unwillingness by the patients to take a (new) NSAID (39%) or acceptable pain level (12%). In 28% no reason could be identified, possibly reflecting inadequate offering of the next step of the protocol by the treating physician. Other reasons for not switching to a (new) NSAID were: contra-indication (7%) and start of different pharmacological treatment (14%).

In conclusion, prescription of paracetamol and prescription of a NSAID after insufficient results with paracetamol seems appropriate in patients with severe knee and/or hip OA, even after prior consideration for joint replacement. The results of switching to a second NSAID after failing paracetamol and a NSAID are disappointing.

## CHAPTER 6

In Chapter 6 of this thesis, a study on fatigue in knee and/or hip OA is presented. Clinical practice and a few studies performed on fatigue and OA suggest that fatigue is a common complaint of patients suffering from OA. The study in Chapter 6 aimed to answer the

question whether fatigue in knee and/or hip OA patients is reduced by standardised conservative treatment as recommended by the treatment guidelines for knee and hip OA. Moreover, the relationships between fatigue and pain and fatigue and physical function were investigated.

A total of 231 patients with knee and/or hip OA were included in this study. The study patients experienced increased fatigue in two of the four domains of fatigue: fatigue severity and fatigue during activity. A total of 47% of patients experienced severe fatigue at baseline (i.e. fatigue levels comparable with patients with chronic fatigue syndrome). After 12 weeks standardised conservative treatment, a small but significant decrease of fatigue severity and fatigue during activity was measured. In the cross-sectional model physical function was independently associated with fatigue severity, whereas pain was independently related to fatigue during activity. Change in fatigue severity was independently related to improvement of physical function, whereas change in fatigue during activity was independently related to reduction of pain and improvement of physical function.

Regarding the underlying mechanism of fatigue in OA, the presented data suggest that fatigue severity is partly determined by physical function, whereas fatigue during activity is determined by both physical function and pain. These associations where found in both the cross-sectional as well as in the longitudinal analyses.

In conclusion, fatigue is common in secondary care knee and hip OA. Conservative treatment as recommended by evidence-based guidelines results in a modest improvement of fatigue levels. Finally, change in fatigue is related to change in pain and physical function.

# MAIN CONCLUSIONS OF THIS THESIS

The main conclusions of this thesis are:

» The majority of individuals with early knee and/or hip OA report persisting health care utilization for OA during two years. (**Chapter 2**)

» Future use of OA-related health care in early knee and/or hip OA is highly variable but predictable to a certain extent. (**Chapter 2**)

» Doxycycline has no symptom-modifying effect in patients with symptomatic knee OA, but is associated with an increased risk of adverse events. (**Chapter 3**)

» The majority of patients with knee and hip OA referred to secondary care (81%) was insufficiently conservatively treated in primary care in The Netherlands. (**Chapter 4**)

» Evidence-based tailored conservative treatment using a standardised protocol is successful in 47% of secondary care knee and/or hip OA patients. (**Chapter 4**)

» Response to evidence-based tailored conservative treatment using a standardised protocol is largely not predictable. Therefore, these treatments should be offered to all patients. (**Chapter 4**)

» Protocolised prescription of paracetamol and the first NSAID after failing paracetamol results in moderate treatment response percentages, but the result of the second NSAID is disappointing in patients with advanced knee and/or hip OA. (**Chapter 5**)

» The treatment response to analgesics in knee and/or hip OA is predictable to a certain extent. (**Chapter 5**)

» High levels of fatigue are very common in patients suffering from knee and/or hip OA in secondary care. (**Chapter 6**)

» Evidence-based tailored conservative treatment leads to a small reduction of fatigue levels, with change in fatigue severity being related to physical function and change in fatigue during activity being related to pain and physical function. (**Chapter 6**)

# 8

# GENERAL DISCUSSION

The aim of this thesis was to improve the conservative treatment of knee and hip osteoarthritis (OA). In this chapter the main findings of the studies presented in this thesis, their clinical implications and future research will be discussed.

# MAIN FINDINGS, CLINICAL IMPLICATIONS AND FUTURE RESEARCH

## Health care utilization

The results of our study on health care utilization (HCU) in early knee and hip OA indicate that a variety of health care resources are used over a two-year period and that HCU is variable between subjects. Although HCU in OA is known to be highly variable,[1-12] predictors for future HCU were not described before. The strongest predictor we were able to identify was previous HCU, rather than disease related variables as pain and limitations in activity. Moreover, around 10% of the early OA patients had already attended a caregiver in secondary care, despite the fact that the majority of patients did not attend an allied health care provider or used pharmacological treatment. The results suggest that education of patients and caregivers on appropriate treatment options for OA might result in more appropriate stepped-care future HCU.

## Evidence-based conservative treatment

As indicated by the studies presented in Chapter 4 and 5, multimodal treatment according to the existing guidelines[13-16] improves the symptoms of patients with knee and hip OA. Even in secondary care knee and hip OA patients, already considered for joint replacement, nearly 50% of patients reached an OMERACT-OARSI response[17] using a short term, simple standardised and feasible treatment protocol. Because a treatment response is not predictable, every patient with symptomatic knee and/or hip OA referred to secondary care should first be treated conservatively before considering joint replacement. However, to tailor treatment future research should focus on identifying predictors for response to treatment. Then, treatment can be tailored to individuals with the best chance to respond. With this approach, unnecessary prescription of potential toxic agents[18;19] could be prevented. Another approach to reduce adverse events is the development of cyclooxygenase-inhibiting nitric oxide donators (CINODSs). This new class of drugs combines a parent non-steroidal anti-inflammatory drug (NSAID) with nitric oxide, with the aim of reducing potential toxicity of the parent drug while maintaining the analgesic and anti-inflammatory effects. Results of a few studies on CINODs in OA are promising as they indeed indicate less adverse events compared to NSAIDs, while maintaining efficacy.[20;21]

To improve the results of conservative treatment, research should be focussed on improvement of the treatment strategy. As pharmacological pain management strategies have not been published before, we cannot compare our results. Perhaps, implementation of weak opioids[22] or intra-articular steroid injections[23] should be applied in the pain management strategy in OA. Moreover, a trial period of 4 weeks for an analgesic might be too long and could therefore be shortened.[24] Another point to consider is the appropriateness of a cut-off point NRS pain $\leq 4$ for each individual patient, because we

found that a substantial part of the patients was satisfied even with a NRS pain > 4. It may be worthwhile to explore the feasibility of individualized cut-off points. Additionally, barriers for use of analgesics - e.g. cognitive or emotional factors could play a role - should be investigated.

The results of conservative treatment in knee and hip OA might be improved further by the development and implementation of effective interventions to motivate patients to adhere to treatment and to apply the advised life style changes, as the results of the study described in Chapter 4 indicate that only a minority of the obese patients actually looses weight despite the advices from the caregiver.

We found in our studies that the vast majority of patients had not been adequately treated with conservative modalities in primary care before referral to secondary care for joint replacement. These findings are in concordance with some earlier studies on adherence to treatment guidelines for knee OA.[25;26] Thus, efforts should be made to improve adherence to evidence-based treatment guidelines for OA. A first step is already made since the multidisciplinary patient-centred stepped-care strategy for conservative treatment of hip or knee OA (i.e. BART) was proposed by a leading expert panel in The Netherlands.[27] At this moment this strategy is implemented in primary care in a research setting. Hopefully, this approach will lead to more timely and appropriate referrals to secondary care and to a reduction of undesirable use of secondary care treatment options, because even in early knee and/or hip OA high secondary care consumption is reported while simple first line treatment options were underutilized.

## Fatigue

The study in Chapter 6 shows that fatigue is a common complaint in patients suffering from knee and hip OA. This is in concordance with the few prior studies on fatigue in OA[28-30] and comparable to inflammatory diseases like rheumatoid arthritis.[31] Our study - although uncontrolled - indicated that standardized evidence-based conservative treatment results in a modest reduction of fatigue levels. Only one other treatment study on fatigue in OA has been published, which shows no effects of a self-management program on fatigue levels.[32]

Our data and data from another study[33] suggest that fatigue severity is partly determined by physical function and not by pain. In contrary, physical fatigue is determined by both physical function and pain. This indicates that fatigue severity and pain as well as the different dimensions of fatigue have different underlying mechanisms. Moreover, fatigue is determined by other variables, like depressive symptoms and coping strategies. However, a recent paper suggests that depressive mood is an intermediate variable in the relation between pain/physical function and fatigue.[33] Future studies are necessary to explore the link between OA and fatigue, to be able to further modify OA-related fatigue.

## New treatment options

As reported in Chapter 6, doxycycline failed to show symptom-modifying effects in knee OA, although the only earlier study in human OA demonstrated structure-modifying effects and suggested some symptom-improving effects.[34] Besides being able to reduce

structural disease progression, a disease-modifying OA drug (DMOAD) should preferably exhibit symptom-modifying properties, since structural (radiographic) abnormalities only modestly correlate with OA-related symptoms.[35;36] Therefore, efforts should be made to unravel the mechanisms underlying symptoms in OA. Probably, other structural abnormalities than radiographic signs are more correlated with patient's complaints. A novel possibility to reduce OA-related pain is inhibiting nerve growth factor, which is increasingly expressed in inflamed tissue. Although the results on pain reduction in the first studies with antibodies to nerve growth factor were impressive, some reports of severe adverse events urge to caution.[37-39]

Finally, modern imaging techniques like ultrasonography[40] and magnetic resonance imaging (MRI)[41] could possibly link structural abnormalities with the symptoms of the individual patient and probably bring in novel treatment targets and the opportunity to tailor the management for individuals with OA.

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# 9

# NEDERLANDSE SAMENVATTING

# INTRODUCTIE

Artrose (in de Engelstalige literatuur: Osteoarthritis (OA)) is de meest voorkomende reumatische aandoening en manifesteert zich vaak in de knie of heup. Geschat wordt dat artrose van de knie en heup bij respectievelijk 74 per 1000 en 56 per 1000 individuen voorkomt in de leeftijdscategorie van 60-64 jaar in Nederland. Artrose wordt gekenmerkt door een disbalans tussen de aanmaak en afbraak van gewrichtskraakbeen. Echter, ook andere structuren in het gewricht blijken betrokken te zijn bij artrose, zoals het gewrichtsslijmvlies (synovium), het onderliggende (subchondrale) bot, pezen, spieren en slijmbeurzen. Daarom wordt artrose tegenwoordig als een aandoening van het gehele gewricht gezien.

Het precieze ontstaansmechanisme van artrose is onbekend. Belangrijke risicofactoren voor het ontstaan van artrose zijn: leeftijd, vrouwelijk geslacht, familiair voorkomen, aangeboren afwijkingen, overgewicht, gewrichtsschade en overmatige belasting van het gewricht in het verleden. Risicofactoren voor progressie van artrose zijn onder andere: standsafwijkingen, spierzwakte en overgewicht. De klachten van artrose bestaan met name uit pijn, stijfheid en beperkte beweeglijkheid van de gewrichten en variëren sterk van persoon tot persoon, maar ook binnen een persoon. Röntgenfoto's kunnen gewrichtsspleetversmalling, botuitgroeiingen (osteofyten), verdichting van het onderliggende bot (subchondrale sclerose) en cysten tonen. Echter, de radiologische afwijkingen komen vaak niet overeen met de klachten van de patiënt, zodat de diagnose vaak zonder het maken van een röntgenfoto wordt gesteld. Bloedonderzoek is in de regel niet afwijkend bij artrose.

Omdat er tot op heden nog geen behandelingen beschikbaar zijn die het artroseproces kunnen beïnvloeden, richt de behandeling van artrose zich op het verminderen van de symptomen van artrose. De aanbevelingen die gedaan worden in de beschikbare *evidence-based* richtlijnen bestaan uit conservatieve (niet-chirurgische) en chirurgische behandelopties. De conservatieve behandelopties bestaan uit niet-farmacologische en farmacologische behandelingen. Niet-farmacologische behandelingen voor knie- en heupartrose bestaan uit educatie, leefstijladviezen, fysiotherapie (spierversterking en conditieverbetering) en indien er sprake is van overgewicht, het advies om af te vallen. De farmacologische behandelopties bestaan met name uit het voorschrijven van paracetamol en ontstekingsremmende pijnstillers (NSAIDs), en eventueel zwakwerkende opioïden en injecties met corticosteroïden. De chirurgische behandeling van knie- en heupartrose bestaat vooral uit gewrichtsvervangende operaties. In het algemeen wordt geadviseerd een gewrichtsvervangende operatie pas uit te voeren indien er onvoldoende resultaat is van de conservatieve behandeling. Een nadeel van een gewrichtsvervanging is dat de prothese vaak na 10-15 jaar vervangen moet worden, waardoor deze ingreep niet aantrekkelijk is voor relatief jonge patiënten met knie- of heupartrose. Tevens blijkt ongeveer één op de zes patiënten die een gewrichtsvervanging heeft ondergaan niet tevreden te zijn met het uiteindelijke resultaat en bovendien is er een kans op perioperatieve complicaties.

Gezien de toename van het aantal mensen met artrose en bovengenoemde nadelen van een gewrichtsvervangende operatie wordt de vraag om effectieve conservatieve behandeling van knie- en heupartrose steeds groter. Uit eerder verricht onderzoek blijkt

tevens dat conservatieve behandelopties van knie- en heupartrose vaak onvoldoende benut worden. Het doel van dit proefschrift was daarom het verbeteren van de conservatieve behandeling van knie en heupartrose. Dit bestond onder andere uit de volgende onderdelen:

» het beschrijven van artrose-gerelateerd zorggebruik en het voorspellen van toekomstig zorggebruik van patiënten met beginnende knie en/of heupartrose
» het onderzoeken van het effect van doxycycline op de symptomen van knieartrose
» het onderzoeken van het resultaat van het toepassen van een op de richtlijnen gebaseerd behandelprotocol voor knie- en/of heupartrose
» het onderzoeken van het voorkomen van vermoeidheid bij patiënten met knie- en/of heupartrose en het effect van het toepassen van het behandelprotocol op de mate van vermoeidheid

## HOOFDSTUK 2

In Hoofdstuk 2 wordt een studie beschreven naar het artrose-gerelateerd zorggebruik van patiënten uit het Cohort Heup En Cohort Knie (CHECK), een landelijke studie waarin 1002 individuen met vroege heup- en knieartrose gedurende 10 jaar worden gevolgd. Voor het onderzoek in Hoofdstuk 2 werden de *baseline* en twee-jaars data gebruikt. Er werden zes vormen van artrose-gerelateerd zorggebruik onderscheiden: gebruik van pijnstillers en voedingsupplementen, contact met de huisarts, een paramedicus of een hulpverlener in de tweede lijn en alternatieve zorg. Middels de *median-split* methode werden veel-gebruikers geïdentificeerd. Patiënten die zowel op *baseline* als na twee jaar geen zorggebruik rapporteerden werden aangemerkt als persisterende geen-gebruikers. De resultaten tonen dat de meerderheid van de patiënten artrose-gerelateerd zorggebruik rapporteerde en dat er geen verschil was tussen de patiënten met beginnende knieartrose en patiënten met beginnende heupartrose. Na twee jaar was het aantal contacten met hulpverleners afgenomen terwijl het gebruik van pijnstillers gelijk bleef. Verminderde fysieke gezondheid en eerder gebruik van zorg bleken de sterkste voorspellers veel zorggebruik in de toekomst. Minder stijfheid, betere fysieke gezondheid en grotere bewegingsuitslagen van de gewrichten waren voorspellers voor geen-zorggebruik na twee jaar.

## HOOFDSTUK 3

Hoofdstuk 3 van dit proefschrift beschrijft een placebogecontroleerde gerandomiseerde geblindeerde studie naar het effect van doxycycline op de symptomen bij patiënten met knieartrose. Tot op heden zijn er geen geneesmiddelen waarvan het onomstotelijk is vastgesteld dat zij het artrose-proces kunnen beïnvloeden (de zogenaamde *Disease Modifying Osteoarthritis Drugs* (DMOADs)). Er zijn echter wel een aantal middelen waarvan gedacht wordt dat zij deze eigenschap bezitten. Doxycycline, een bekend antibioticum, is een van deze geneesmiddelen. Doxycycline blijkt in een eerdere studie de progressie van radiologische afwijkingen van knieartrose te remmen. Onbekend was echter of dit middel daarnaast ook in staat is om de klachten van artrose te verminderen.

In het onderzoek onder 232 patiënten met knieartrose, beschreven in Hoofdstuk 3, werd geen verschil gevonden tussen patiënten behandeld met doxycycline en patiënten behandeld met placebo voor wat betreft afname van klachten na 24 weken. In totaal bereikten 72 van de 232 deelnemers een behandelrespons (OMERACT-OARSI respons) na 24 weken behandeling. Echter, het aantal responders was niet verschillend tussen beide behandelgroepen. Ook werd er geen verschil gevonden in verbetering van pijn, stijfheid, fysiek functioneren en globale inschatting van de ziektetoestand door patiënten. Wel bleken er meer patiënten in de doxycycline-groep last te hebben van bijwerkingen (met name zonlichtovergevoeligheid) en staakten meer mensen in de doxycycline-groep het onderzoek voortijdig wegens bijwerkingen vergeleken met individuen in de placebo-groep. Geconcludeerd kan worden dat doxycycline geen effect heeft op het verbeteren van klachten gerelateerd aan knieartrose, maar wel een verhoogde kans op bijwerkingen geeft.

## HOOFDSTUK 4

Hoewel de behandelingen die geadviseerd worden in de richtlijnen voor de conservatieve behandeling van knie- en heupartrose allen bewezen effectief blijken te zijn in klinische studies, was het resultaat van het gecombineerd toepassen van deze adviezen niet bekend. Daarom werd in de studie die wordt beschreven in Hoofdstuk 4 van dit proefschrift, het resultaat van een op *evidence-based* richtlijnen gebaseerd behandelprotocol onderzocht bij 183 patiënten met knie- en/of heupartrose. Het protocol bestond uit educatie, leefstijladviezen, verwijzing naar de fysiotherapeut voor spierversterking en conditieverbetering, het advies om af te vallen indien er sprake was van overgewicht en het stapsgewijs voorschrijven van pijnstillers. Het voorschrijven van pijnstillers werd gebaseerd op de mate van pijn gemeten middels een *numeric rating scale* pijnscore (0-10, waar 10 maximaal ervaren pijn betekent). Indien de pijnscore > 4 was werd de volgende stap in het voorschrijven van pijnstillers genomen. Als eerste stap gold het voorschrijven van paracetamol, gevolgd door een NSAID, eventueel gevolgd door het wisselen van de NSAID. Indien nodig (pijnscore > 4) werd als vierde stap tramadol voorgeschreven. Patiënten kwamen op *baseline* en na 12 weken op de polikliniek en werden na 4 en na 8 weken gebeld om zo nodig de pijnmedicatie aan te passen. Na 12 weken conservatieve behandeling bleken 86 van de 183 (47%) patiënten te voldoen aan de OMERACT-OARSI responder criteria en hadden 71 van de 183 (39%) patiënten een pijnscore ≤ 4. Tevens werden er duidelijke verbeteringen gezien in pijn, fysiek functioneren en globale inschatting van de ziektetoestand door patiënten.

Een behandelrespons na 12 weken bleek moeilijk te voorspellen met *baseline* variabelen: de enige geïdentificeerde voorspeller bleek het aantal gebruikte NSAIDs voorafgaand aan het onderzoek te zijn.

Een opvallende bevinding was dat de meerderheid van de patiënten (81%) voorafgaand aan het onderzoek geen adequate conservatieve behandeling had gehad in de eerste lijn, terwijl er in de meerderheid van de gevallen al wel een gewrichtsvervangende operatie overwogen was.

De conclusie die getrokken kan worden is dat het gestandaardiseerd toepassen van de conservatieve behandelingen geadviseerd in de behandelrichtlijnen bij ongeveer de helft van de knie- en heupartrose patiënten in de tweede lijn leidt tot een goede behandelrespons en dat een goede behandelrespons moeilijk te voorspellen is. Dit betekent dat iedere patiënt evenveel kans heeft op een goede behandelrespons en dat adequate conservatieve behandeling aan iedere patiënt met knie- en/of heupartrose zou moeten worden aangeboden alvorens een prothese wordt overwogen.

## HOOFSTUK 5

Omdat er weinig studies gedaan zijn naar farmacologische behandelstrategieën in de conservatieve behandeling van artrose werd een studie verricht (Hoofdstuk 5) naar de resultaten van het voorschrijven van analgetica in de verschillende behandelstappen in het behandelprotocol beschreven in Hoofdstuk 4. De eerste stap was het starten van paracetamol in een dosering van 3 maal daags 1000 mg indien er geen sprake was van recent adequaat gebruik van dit middel. De volgende stap was het starten van een NSAID (NSAID 1) indien de pijnscore > 4 bleef. De derde stap bestond uit het wisselen van NSAID (NSAID 2). In totaal werden er 347 patiënten met knie en/of heupartrose geïncludeerd in de studie, waarvan er 210 met paracetamol, 190 met NSAID 1 en 87 met NSAID 2 behandeld werden, met responspercentages (pijnscore ≤ 4) van respectievelijk 25, 16 en 11. Onafhankelijke voorspellers voor respons op paracetamol waren: hogere leeftijd, mildere globale inschatting van de ziektetoestand door patiënt, minder stijfheid en ernstigere radiologische afwijkingen. Voor respons op NSAID 1 werd de volgende voorspeller geïdentificeerd: mildere globale inschatting van de ziektetoestand door patiënten.

Bij 138 van de 302 (46%) patiënten werd niet van pijnstiller gewisseld, hoewel dit wel werd geadviseerd (pijnscore > 4). In meer dan de helft van deze gevallen was dit de wens van de patiënt. In een minderheid van de gevallen werd er geen reden gevonden voor het niet-switchen van de medicatie en was er dus mogelijk sprake van het niet adequaat aanbieden van de volgende stap van het protocol door de behandelaar.

Concluderend kan gesteld worden dat het voorschrijven van paracetamol en een NSAID na falen van paracetamol leidt tot redelijke responspercentages, terwijl het resultaat van het voorschrijven van een tweede NSAID teleurstellend is.

## HOOFDSTUK 6

Uit de klinische praktijk en uit de weinige wetenschappelijke onderzoeken op dit gebied blijkt dat vermoeidheid een veel voorkomende klacht is van patiënten met artrose. In Hoofdstuk 6 wordt een studie beschreven waarin het voorkomen van vermoeidheid en het resultaat van op de *evidence-based* richtlijnen gebaseerde conservatieve behandeling op de vermoeidheid bij knie- en/of heupartrose patiënten werden onderzocht. Daarnaast werd de relatie tussen vermoeidheid en pijn en tussen vermoeidheid en fysiek functioneren

bestudeerd. Er werden 231 patiënten met knie- en/of heupartrose geïncludeerd in deze studie. De patiënten ervaarden vermoeidheid in verhoogde mate in twee domeinen: vermoeidheid ernst en fysieke vermoeidheid. Bij 47% van de patiënten was er sprake van ernstige vermoeidheid, dat wil zeggen mate van vermoeidheid vergelijkbaar met patiënten met het chronisch vermoeidheidssyndroom. Na 12 weken conservatieve behandeling werd er een kleine maar significante verbetering gemeten van de vermoeidheid ernst en fysieke vermoeidheid. Fysiek functioneren was cross-sectioneel geassocieerd met ernst van vermoeidheid, terwijl pijn cross-sectioneel geassocieerd was met fysieke vermoeidheid. Verandering van ernst van vermoeidheid was onafhankelijk geassocieerd met verandering van fysiek functioneren, terwijl verandering van fysieke vermoeidheid was geassocieerd met verandering van pijn en verandering van fysiek functioneren.

Geconcludeerd kan worden dat conservatieve behandeling zoals aanbevolen wordt in de richtlijnen resulteert in een kleine verbetering van vermoeidheid bij patiënten met knie- en/of heupartrose. Daarnaast lijkt vermoeidheid ernst gerelateerd aan fysiek functioneren en fysieke vermoeidheid aan pijn en fysiek functioneren.

## CONCLUSIES

» De meerderheid van de patiënten met vroege knie- en/of heupartrose rapporteert persisterend gebruik van artrose-gerelateerde zorg gedurende twee jaar. (**Hoofdstuk 2**)
» Toekomstig geen-gebruik en veel-gebruik van artrose-gerelateerde zorg zijn tot op zekere hoogte te voorspellen. (**Hoofdstuk 2**)
» Doxycycline heeft geen effect op de symptomen van knieartrose, maar geeft wel bijwerkingen. (**Hoofdstuk 3**)
» De meerderheid (81%) van de knie- en/of heupartrose patiënten in de tweede lijn, veelal zonder een indicatie voor chirurgisch ingrijpen, heeft onvoldoende conservatieve behandeling gekregen in de eerste lijn.
» *Evidence-based* conservatieve behandeling van knie- en/of heupartrose volgens een gestandaardiseerd protocol was succesvol bij 47% van knie- en/of heupartrose patiënten in de tweede lijn. (**Hoofdstuk 4**)
» Het geprotocolleerd voorschrijven van paracetamol en een NSAID na falen van paracetamol is succesvol in 25% van de gevallen, terwijl het wisselen van een NSAID teleurstellend is bij patiënten met knie- en/of heupartrose in de tweede lijn. (**Hoofdstuk 5**)
» De respons op analgetica bij patiënten met knie- en/of heupartrose in de tweede lijn is enigszins te voorspellen. (**Hoofdstuk 5**)
» Ernstige vermoeidheid komt veel voor bij patiënten met knie- en/of heupartrose in de tweede lijn.
» Geprotocolleerde *evidence-based* conservatieve behandeling van knie- en/of heupartrose in de tweede lijn leidt tot een kleine verbetering van vermoeidheid. Verandering van vermoeidheid ernst is gerelateerd aan verandering van fysiek functioneren, terwijl verandering van fysieke vermoeidheid gerelateerd is aan verandering van pijn en fysiek functioneren. (**Hoofdstuk 6**)

LIST OF PUBLICATION AND PRESENTATIONS

CURRICULUM VITAE

DANKWOORD

# LIST OF PUBLICATIONS AND PRESENTATIONS

## Articles

**Snijders GF**, den Broeder AA, Bevers K, Jeurissen ME, van Eerd JE, van den Hoogen FHJ. Measurement characteristics of a new rapid anti-CCP2 test compared to the anti-CCP2 ELISA. *Scandinavian Journal of Rheumatology* 2008; 37: 151-4.

van den Bemt BJ, den Broeder AA, **Snijders GF**, Hekster YA, van Riel PLCM, Benraad B, Wolbink GJ, van den Hoogen FHJ. Sustained effect after lowering high-dose infliximab in patients with rheumatoid arthritis: a prospective dose titration study. *Annals of the Rheumatic Diseases* 2008; 67: 1697-701.

**Snijders GF**, den Broeder AA, van Riel PLCM, Straten VHHP, de Man FHR, van den Hoogen FHJ, van den Ende CHM, on behalf of NOAC study group. Evidence-based tailored conservative treatment of knee and hip OA: between knowing and doing. *Scandinavian Journal of Rheumatology* 2011; 40: 225-31.

**Snijders GF**, van den Ende CHM, van Riel PLCM, van den Hoogen FHJ, den Broeder AA, on behalf of NOAC study Group. The effects of doxycycline on reducing symptoms in knee osteoarthritis: results from a triple-blinded randomised controlled trial**.** *Annals of the Rheumatic Diseases* 2011; 70: 1191-96.

**Snijders GF**, van den Ende CHM, Fransen J, van Riel PLCM, Stukstette MJPM, Defoort KC, Arts-Sanders MA, van den Hoogen FHJ, den Broeder AA, on behalf of NOAC study group. Fatigue in knee and hip osteoarthritis: the role of pain and physical function. *Rheumatology* E-pub ahead of print.

Hoogeboom TJ, **Snijders GF**, Cats HA, de Bie RA, Bierma-Zeinstra SMA, van den Hoogen FHJ, van Riel PLCM, Emans PJ, Wesseling J, den Broeder AA, van den Ende CHM. Predictors of health care utilization in patients with early osteoarthritis: results from the CHECK cohort. *Submitted.*

**Snijders GF**, van den Ende CHM, van den Bemt BJF, van Riel PLCM, van den Hoogen FHJ, den Broeder AA, on behalf of NOAC study group. Treatment outcomes of a Numeric Rating Scale-guided pharmacological pain management strategy in symptomatic knee and hip osteoarthritis in daily clinical practice. *Submitted.*

## Oral presentations

Wetenschappelijke vergadering Nederlandse Vereniging voor Reumatologie, Veldhoven, 2007: Meetkarakteristieken van een nieuwe anti-CCP2 sneltest vergeleken met de anti-CCP2 ELISA.

International Congress on Autoimmunity, Porto, Portugal, 2008: Measurement characteristics of a new anti-CCP2 quick test compared to the anti-CCP2 ELISA

Annual European Congress of Rheumatology (EULAR), London, United Kingdom, 2011: Doxycycline has no symptom modifying effects in knee osteoarthritis: results from a randomised placebo-controlled trial

## Poster presentations

Osteoarthritis Research Society International (OARSI) congress, Rome, Italy, 2008: Twelve weeks multimodal conservative treatment of knee osteoarthritis using a newly developed treatment protocol in The Netherlands: preliminary results

Wetenschappelijke vergadering Nederlandse Vereniging voor Reumatologie, Arnhem, 2008: Twaalf weken conservatieve behandeling van knie- en heupartrose volgens de nieuwe CBO-richtlijn: eerste resultaten

Osteoarthritis Research Society International (OARSI) congress, Brussels, Belgium, 2010: Evidence-based tailored conservative treatment of knee and hip OA: between knowing and doing

Wetenschappelijke vergadering Nederlandse Vereniging voor Reumatologie, Arnhem, 2010: Vermoeidheid bij knie- en heupartrose

Annual European Congress of Rheumatology (EULAR), Rome, Italy, 2010: Results of standardised NRS guided conservative treatment of knee and hip OA and predictors for response

Annual European Congress of Rheumatology (EULAR), London, United Kingdom, 2011: Fatigue in knee and hip osteoarthritis: the role of pain and physical function

# CURRICULUM VITAE

Gijsbreght Frederik Snijders werd op 9 februari 1981 geboren te Nijmegen en groeide op in Almelo. Hij doorliep de gehele Vrije School en behaalde in 2000 zijn VWO diploma aan het Baudartius College in Zutphen. Gijs begon in 2000 de studie Geneeskunde aan de Radboud Universiteit in Nijmegen, alwaar hij in 2007 zijn artsexamen behaalde.

De liefde voor de Reumatologie ontstond tijdens zijn introductie-co-schap eind 2004 op het Reumacentrum van de Sint Maartenskliniek te Nijmegen onder leiding van Dr. M.J.A.M. Franssen. Dit kreeg een vervolg met een keuze-co-schap in juni 2006, opnieuw onder leiding van Dr. M.J.A.M. Franssen.

Gijs deed zijn eerste onderzoekservaring op tijdens de wetenschappelijke stage in het kader van de studie Geneeskunde in het najaar van 2006, getiteld: 'Afbouwen van hoge doses TNF-$\alpha$-blokkers in reumatoïde artritis', onder leiding van dr. A.A. den Broeder. Deze samenwerking resulteerde in de start van een promotieonderzoek in maart 2007 met als onderwerp 'Conservatieve behandeling van knie- en heupartrose' op het Reumacentrum van de Sint Maartenskliniek onder leiding van dr. A.A. den Broeder, dr. C.H.M. van den Ende en prof. dr. P.L.C.M. van Riel (UMC St Radboud). De resultaten van dit onderzoek staan beschreven in dit proefschrift.

In zijn jeugd voetbalde Gijs bij s.v. PH Almelo. Sinds het seizoen 2001-2002 komt hij uit voor de Nijmeegse zaterdag-derdeklasser Uni v.v.

Vanaf april 2011 is Gijs begonnen met de vooropleiding Interne Geneeskunde in het Canisius Wilhelmina Ziekenhuis te Nijmegen (opleider dr. A.S.M. Dofferhoff) in het kader van de opleiding tot reumatoloog (opleider prof. dr. P.L.C.M. van Riel).

# DANKWOORD

Het voltooien van mijn promotietraject was me nooit gelukt zonder de hulp van velen die ik hierbij allemaal hartelijk dank. Daarnaast was het onderzoek niet mogelijk zonder de vele knie- en heupartrose patiënten die bereid waren deel te nemen aan de onderzoeken beschreven in dit proefschrift. Een aantal belangrijke personen wil ik apart bedanken.

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